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Abstract	•	•			:			
The present invention counds are inhibitors of	provides compounds, more retroviral proteases and are	particula useful	arly dipeptide for treating di	analogs, which seases related	bind to retrov to infection by	riral proteas retrovirus	ses. These	
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The present invention relates to retroviral protease inhibitor compounds, pharmaceutical compositions thereof, anda method of treating retroviral diseases therewith, including a method of treating disease states associated with human immunodeficiency virus (HIV-1, HIV-2). Retroviruses, that is, viruses within the family of Retroviridae, are a class of viruses which transport their genetic material as ribonucleic acid rather than deoxyribonucleic acid. Also known as RNA-tumor viruses, their presence has been associated with a wide range of diseases in humans and animals. They are believed to be the causative agents in pathological states associated with infection by Rous sarcoma virus (RSV), murine leukemia virus (MLV), mouse mammary tumor virus (MMTV), feline leukemia virus (FeLV), bovine leukemia virus (BLV), Mason-Pfizer monkey virus (MPMV), simian sarcoma virus (SSV), simian acquired immunodeficiency syndrome (SAIDS), human Tlymphotropic virus (HTLV-I, -II) and human immunodeficiency virus (HIV-1, HIV-2), which is the tiologic agent of AIDS

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(acquired immunodeficiency syndrome) and AIDS related complexes, and many others. Although the pathogens have, in many of these cases, been isolated, no effective method for treating this type of infection has been developed.

Retroviral replication occurs only in host cells. Critical to this replication is the production of functional viral proteins. Protein synthesis is accomplished by translation of the appropriate open reading frames into polyprotein constructs, which are processed, at least in part, by a viral protease into the functional proteins. proteolytic activity provided by the viral protease in processing the polyproteins cannot be provided by the host and is essential to the life cycle of the retrovirus. In fact, it has been demonstrated that retroviruses which lack the protease or contain a mutated form of it, lack infectivity. See Katoh et al., Virology, 145, 280-92(1985), Crawford, et al., J. Virol., 53, 899-907 (1985) and Debouk, et al., Proc. Natl. Acad. Sci. USA, 84, 8903-6(1987). Inhibition of retroviral protease, therefore, presents a method of therapy for retroviral disease.

The use of isosteric replacements has been disclosed as a strategy for the development of protease inhibitors for HIV-1. European Patent Applications EP-A 337 714, EP-A 357 332, EP-A 346 847, EP-A 342 541, EP-A 352 000, EP-A 393 445 and EP-A 434 365 are representative, and are incorporated These references disclose dipeptide herein by reference. analogs of the natural polyprotein substrates of retroviral proteases. As discussed therein, these dipeptide analogs bind selectively and competitively to retroviral proteases; however, the protease is unable to cleave the carbon-carbon bond presented to it instead of the scissile amide bond of the natural substrate. Thus, such compounds are useful for inhibiting viral replication by inactivation of the protease. The incorporation of heterocyclic elements in the P3' and P4' substrate positions of compounds containing a dipeptide isostere has been disclosed by deSolms et al., J. Med. Chem., 34, 2852 (1991). Howev r, these compounds can be less than desirable for obtaining optimal drug delivery in mammalian

organisms, particularly in humans. Some of these compounds can also have a less than desirable serum half-life, and therefore duration of action, because they contain amide bonds in relatively high proportion, and thus are prone to metabolic degradation, hepatic clearance, or other elimination mechanisms.

There exists a need for novel compounds which inhibit retroviral protease activity, and a need for compounds which possess desirable pharmacokinetic properties for good drug delivery and metabolic stability for good serum half-life and duration of action. Such pharmaceutical uses provide therapies for retroviral diseases in mammals, especially in humans, which have been heretofore difficult to treat.

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SUMMARY OF THE INVENTION

The present invention provides compounds, hereinafter represented as formula (I), which bind to retroviral proteases. These compounds are inhibitors of retroviral proteases and are useful for treating diseases related to infection by retroviruses.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier.

The present invention additionally provides a method for treating retroviral disease, comprising administering to a mammal in need thereof an effective amount of a compound of formula (I): (194) DO (104 144) (1

30 (C S) O CERT C DETAILED DESCRIPTION OF THE INVENTION to the terminal factor of the first of the factor of

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only le dess The compounds of the present invention are illustrated by formula (I):

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wherein:

R1 and R3 are each independently Q, Q-C1-6alkyl, 5 Q-C2-6alkenyl, Q-C2-6alkynyl or C1-6alkyl substituted by one to five fluorine atoms, each optionally substituted by R²³; Q is H, C3-6cycloalkyl, C5-6cycloalkenyl, Ar or Het

R2 is H or OH; Ball to location between the

R4 is R6-NR11- or CONR11CHR6R7 1/4 20 1 1/4 10 6 10

R5 is R6-NR11 or R102NR11 or astes at R⁸ de de ven ent la consegu

X is NR¹¹, O or S;

 R^7 is Q, Q-C₁₋₆alkyl or Q-C₂₋₆alkenyl;

 \mathbb{R}^8 and \mathbb{R}^9 are each independently H, OH, halo, \mathbb{N}_{02} , \mathbb{C}_{0R}^{12} , CF3, Ar, C_{1-6} alkyl- R^{15} , or $R^{17}(R^{18}R^{19}C)_{m}$, or together form a

fused C2-4alkylene, aryl or heteroaryl moiety;

 R^{10} is $A-(B)_{n}-;$

. Rest to ye for you actuating. R¹¹ is H or C₁₋₄alkyl;

R12 is R7, OR7, NR7R11 or an amino acid or amino alcohol;

B is an amino acid; id it as a yell the me according A is H, Ar, Het, $R^{17}(R^{18}R^{19}C)_m$, Ar-W, Het-W or R17 (R18R19C) m-W, or phthaloyl each optionally substituted by one to three groups chosen from R15 or C1-6alkyl-R15;

W is C=0, OC(=0), $NR^{11}C(=0)$, SC(=0), $NR^{11}C(=S)$, SO_2 ,

 $NR^{11}SO_2$ or $P(=0)(OR^{22})$;

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 R^{15} is H, nitro, C_{1-6} alkoxy, C_{1-6} alkylthio, $O(C=0)R^{16}$, C=OR²², CO₂R²², CON(R¹⁶)₂, N(R²²)₂, NHC(=N)NH-A, I, Br, Cl, F, OR10, or OH, provided that when R15 is a substituent of the carbon adjacent to W, R15 is not halogen or OH when W is OC (=O) or NHCO;

R¹⁶ is H or C₁₋₆alkyl;

 ${\bf R^{17}},~{\bf R^{18}}$ and ${\bf R^{19}}$ are independently: i) H, ${\bf R^{15}}$ or C_{1-4} alkyl, C_{2-6} alkenyl, phenyl, naphthyl, C_{3-6} cycloalkyl or Het, each optionally substituted by one to three R15 or

joined together to form a phenyl, naphthyl, C3-6cycloalkyl or Hetiring, or iii) R¹⁷ is as above and R¹⁸ and R¹⁹ together are named =0; and have a phenyl, naphthyl, C3-6cycloalkyl or Hetiring, or iii) R¹⁷ is as above and R¹⁸ and R¹⁹ together are

 R^{22} is $H_{*,9}C_{1-6}$ alkyl, phenyl or phenyl- C_{1-4} alkyl; R^{23} is $-X'-(CH_2)_qNR^{24}R^{25}$, X'' [((CH₂)_rO)₈] R^{26} ,

The Ro CH₂X"[((CH₂)_rO)_s]R²⁶, or benzofuryl, indolyl, azacycloalkyl, simmed azabicyclo₁C₇₋₁₁cycloalkylsor benzopiperidinyl, optionally acos, substituted with C₁₋₄alkyl;

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s is 1-6 and rais 1-3 within each repeating unit s;

(3) X" is CH2, NR', O, S, SO or SO2;

 $\mathbb{C}^{R^{24}}$ and \mathbb{R}^{25} are i) \mathbb{C}_{1-6} alkyl, optionally substituted by OH, \mathbb{C}_{1-3} alkoxy, or $\mathbb{N}(\mathbb{R}^*)_2$, ii) the same or different and

joined together to form a 5-7 member heterocycle containing up to two additional heteroatoms selected from NR, 0, S, SO, SO2, said heterocycle optionally substituted with C1-4alkyl,

iii) aromatic heterocycle, optionally substituted with

20 C1-4alkyl-or-N(R')2; Ling Drs & Law Tyris the

weinRivis H ortC1-4alkyl; and mangiores and comment of make

R²⁶ is H, C₁₋₄alkyl, C(=0)R²⁷, C(=0)U[(CH₂)_mO]nR', C(=0) (OM)₂, CO₂R²⁷, C(=0)NR²⁷R²⁸, where M is a mono or discontinuous metal ion, and U is NR' or O;

or more hydroxy, carboxy, halo, C₁₋₃alkoxy, CONR'₂, NR'₂, CO₂R', SO₂NR'₂, CH₂NR₂, NR'COR', NR'SO₂R', X"[(CH₂)_rO]_sR' or CH₂X"[(CH₂)_rO]_sR'; SO₂R', SO₂

R²⁸ is H, C₁-6alkyl or together with R²⁷ forms a 5-7

30 "membered heterocycle or a 6 membered heterocycle containing a heteroatom selected from N, O and S;

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or a pharmaceutically acceptable salt thereof.

Also included in this invention are pharmaceutically vacceptable addition salts, complexes or prodrugs of the compounds of this invention. Prodrugs are considered to be

any covalently bonded carriers which release the active parentidrug according to formulat (I) intvivo. Sealor

Formula (I) is intended to encompass all unique nonracemic stereoisomers which may occur due to the presence of asymmetric carbon atoms in the molecule. Such compounds may occur as pure enantiomers or diastereomers or as a mixture of individual stereoisomers. The definition of any substituent moiety which may occur more than once in formula (I) is independent of any other occurrence succombinations of substituents and/or variables are permissible only if such combinations result in stable compounds: 10 10 10

Compounds of this invention which include acyclic double bonds may be present in either the cis (Z) for trans (E) geometrical configuration with respect to any two

15 a substituents. The self-the to the transfer of the

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on a so we when X is NH, git will be appreciated that the of heterocyclic ring is an imidazole which can undergo A tautomerization. All tautomerics forms: of the simidazole are within the scope of this invention and planars (thi

Suitably R1 and R3 are C1-6alkyl, Ar-C1-6alkyl, S Ar-C₂-6alkenyl, Ar-C₂-6alkynyl, C₁-6alkyl optionally substituted by one to five fluorine atoms or benzyl substituted in the 4-position by R23 Preferably R1 is benzyl and R3 is benzyl, 4-hydroxybenzyl or phenylpropenyl.

25 12 15 Suitably R2 is H. 1915 The Late of the State of The

Suitably X is S or N-R11. SoPreferably XdiscNH. Preferably R4 is CONR11CHR6R7. WHY CHEST I CANCOL Suitably R^5 is R^{10} - NR^{11} . Preferably (R^5) is the property of R^5

butyloxycarbonylamino or isopropyloxycarbonylamino.

Suitably R^7 is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl or benzyl. Preferably R^7 is C_{1-6} alkyl. Isopropyl, is most preferred.

Suitably R⁸ is H, C₁₋₆alkyl, COR¹², NO₂ or Br. Preferably R8 is H. Charles and the following the property of the propert

35 Suitably R9 is H, NO2, Br, COR12, CF3, Ar, C1-6alkylor C_{1-6} alkyl- R^{15} , wherein R^{12} is H, C_{1-6} alkyl, Ar, OC_{1-6} alkyl, NH2, and R¹⁵ is OH. Preferably R^9 is H_0° or COR^{12} . We say

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Suitably B is Ala or Val. Pr ferably m is 0 and B is
      - twin absent, welgo do for your right word of the good
                              Suitably A is Het, R^{17}(R^{18}R^{19}C)_m-W, Ar-W or Het-W.
           Suitably R17, R18 and R19 are H, or C1-4alkyl, Het or Ar
    _{\rm min} 5 m optionally substituted by one or two R<sup>15</sup> or C<sub>1-6</sub>alkyl-R<sup>15</sup>, or
                   (R^{18}R^{19}C) are joind together to form a phenyl, C_{3-6}cycloalkyl
         or pror Hetgring. State Copy data visuality (2015)
            Service Suitably W is C=0, OC(=0), NHC(=0), NHC(=S), or SC(C=0).
                             Suitably R<sup>17</sup> (R<sup>18</sup>R<sup>19</sup>C)<sub>m</sub>- is Ar-CH<sub>2</sub>, Ar, Het, Het-CH<sub>2</sub>,
        10) C1-6alkyl or C3-6cycloalkyl optionally substituted by one to
                  three groups selected from R15. Suitably R15 is OH.
              or (R18R19C) are Het or Ar, Het is suitably quinolinyl,
ming pyridyl, imidazolyl, thiazolyl, tetrahydrothiopyranyl or
                 tetrahydropyranyl, and Ar is phenyl. I donge Latte
                            Suitably R<sup>23</sup> is hydroxy-C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkoxy-
          C_{1-4}alkoxy, or =0 (CH<sub>2</sub>) 2NR<sup>24</sup>R<sup>25</sup>, wherein R<sup>24</sup> and R<sup>25</sup> are are a
     - Post 5- or 6-membered heterocycle, such as morpholino.
                            In one preferred embodiment W is C=O.29 have November 1
           - '1)-(In another: preferred: embodiment: W is:OC(=O).(A))
    -- 20 (gradity) In a third preferred embodiment (R10 is C1-6alkyloC (=0) or
                 C<sub>5-6</sub>cycloalkylOC(=O) substituted by one or two OH or CH<sub>2</sub>OH
          to groups. The fire arms they we do see the day of the to per the
        Representative compounds of this invention are:
                 (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)-
       25 amino-6-phenyl-N-[1'-isopropyl-1'-(4-aminocarbonyl-thiazo-2-
              (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)-
       amino-6-phenyl-N-[1,-isopropyl-1,-(thiazo-2-yl)]methyl-
             -hexanamide; 4-9-1200 day by the space of this country by the
              (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)-
       amino-6-phenyl-N-(15-imidazo-2-yl)methyl-hexanamide
            - Lhydrochloride; typesty-, - Lord melle
                (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)-
      -'() amino-6-phenyl-N-[1'-methyl-1'-(imidazo-2-yl)] methyl-
      35 phexanamide hydrochloride; October 1980 and 1
                (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)-
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amino-6-phenyl-N-[1'-benzyl-1'-(imidazo-2-yl)]methyl-

hexanamide hydrochloride;

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(2R, 4S, 5S, 1'S) -5- (carbobenzyloxy) amino-4-hydroxy-N-(1'-
           isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
                                    7 × 23
                                        Suduandy A is Hat.
           hexanamide:
           (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
          isopropyl-1'-(4,5-dimethyl)imidazol-2-yl]methyl-6-phenyl-2-
          phenylmethyl-hexanamide; of spin base (300 400)
           (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
          isopropyl-1'-(N'-methyl)imidazol-2-yl]methyl-6-phenyl-2-
         phenylmethyl-hexanamide; and (1861, 874) Var y (1862, 864
          (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
          isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(3-9-4)
          phenylpropargyl) hexanamide; 1 1 55% ess. (32 3863) sc
     (2R, 4S, 5S, 1'S) -5- (benzyloxyethoxycarbonyl) amino-4-hydroxy-N-
          (1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2- 03
          phenylmethyl-hexanamide; who by at $28 years and
         (2R, 4S, 5S, 1'S) -5- (methoxycarbonyl) amino-4-hydroxy-N-(1'-
          isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
          hexanamide;
                              in the constant property of the
          (2R, 4S, 5S, 1'S) -5-(ethoxycarbonyl)amino-4-hydroxy-N-(1'-
20 20 isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
                             of the fact of the Compatibility back appared
       hexanamide;
          (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
         isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(3-phenyl-2-
        propenyl) hexanamide; Partigue and used with (UTLICALLER LICE)
  25 (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
         isopropyl-1'-(4-nitroimidazol-2-yl)]methyl-6-phenyl-2-
     phenylmethyl-hexanamide; had all sedg-S- 2 123 (6.2.22)
        (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
         ethyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
- 1.30 hexanamide; A P P by 1.45 man(q-2-12) p.c. (chais)
         (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
        propyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
        hexanamide; who is now diving it was quit ($11,123,03,012)
        (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
        isopropyl-1'-(4-bromoimidazol-2-yl)]methyl-6-phenyl-2-
        phenylmethyl-hexanamide; with a read and applying the con-
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ม เอาเกราะ ช่อ ส่วิเดย รดกาศ

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(2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
                         isopropyl-1'-(4,5-dibromoimidazol-2-yl)]methyl-6-phenyl-2-
                        phenylmethyl-hexanamide; ab an are the state of the state
          (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
    ye. 45 ( isopropyl-1!-(4-methylimidazol-2-yl)]methyl-6-phenyl-2-
                       phenylmethyl-hexanamide;
 -1)-'--(2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'-
                       isopropyl-1'-(4-trifluoromethylimidazol-2-yl)]methyl-6-
                      phenyl-2-phenylmethyl-hexanamide; a person operior of the second of the 
10 (2R, 4S, 5S, 1 S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-methyl-
    Ivel : N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
                     phenylmethyl-hexanamide;
      (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
                     isopropyl-1'-(4-carbomethoxyimidazol-2-yl)]methyl-6-phenyl-2-
                 phenylmethyl-hexanamide;
                                                                                                   The speciment of the particular states of the
                    (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
        -9-0:isopropyl-1!-(4-methylcarbonylimidazol-2-yl)]methyl-6-phenyl-
                    2-phenylmethyl-hexanamide;
        (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
                   isopropyl-14-(4-phenylcarbonyl-imidazol-2-yl)]methyl-6-38
                   phenyl-2-phenylmethyl-hexanamide;
  The Cold (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
 isopropyl-1:-(4-formylimidazol-2-yl)]methyl-6-phenyl-2-
                  phenylmethyl-hexanamide;
                                                                                                         and the analysis.
      25 (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
                  isopropyl-1'-(4-(hydroxymethyl)-imidazol-2-yl)]methyl-6-
          phenyl-2-phenylmethyl-hexanamide;
      (2R,4S,5S,1'S)-5-((tetrahydrothiopyran-4-yl)oxycarbonyl)-
            amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
   30 phenyl-2-phenylmethyl-hexanamide;
            (2R,4S,5S,1!S)-5-((tetrahydro-4H-pyran-4-yl)oxycarbonyl)-
-S-----amino-4-hydroxy-N-(1:1-isopropyl-1'-imidazol-2-yl)methyl-6-
                phenyl-2-phenylmethyl-hexanamide;
                 (2R, 4S, 5S, 1'S) -5-(4-picolinyloxy) amino-4-hydroxy-N-(1'-
  35 misopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
               hexanamide; who was all to be on white
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ो तर्व र पर तेवित्र क्षिष्ट्रद्राष्ट्रकार वार्चन कार कार प्रमुख्य का द्वारा किया गाउँ एक एक प्राप्त कार कार है

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(2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
           isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(4,4,4-
             trifluorobut-1-yl) hexanamide : itam: 1 - 1 vist of vising
           (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
             isopropyl-1'-(4-((1RS)-1-hydroxyethyl)-imidazol-2-yl)]methyl-
             6-phenyl-2-phenylmethyl-hexanamide; snear-fydrydd y ddirection o'r control o'r
           \sim (2R, 4S, 5S, 1'S) = 5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-(1-
            methyl)propyl-1'-(imidazol-2-yl)]methyl-6-phenyl-2-
            phenylmethyl-hexanamide; a new openion only menty of the series of
   10 (2R, 4S, 5S, 1'S) -5-(propylaminocarbonyl) amino-4-hydroxy-N-[1'-
            isopropyl-1'-(imidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-
            hexanamide;
                                                                      con the cared Lydfort wanted
    (2R, 4S, 5S, 1'S) -5-(4-hydroxybutanoyl) amino-4-hydroxy-N-(1'-
         isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-cqcareass.
           phenylmethylhexanamide; (A) The two of vitrous constraints
         (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(benzyloxy-
           carbonyl) valylamino-6-phenyl-N-(1'-isobutyl-1'-imidazo-2-
           yl) methyl-hexanamide;
                                                                 that was the Hyposinightalest
      (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(N-acetylvalyl)-
          amino-6-phenyl-N-(1'-isobutyl-1'-imidazo-2-yl)methyl-
          hexanamide;
                                                    that was an age to the property by aday a
         (2R, 4S, 5S, 1'S) -5-[(imidazol-2-yl)methyloxycarbonyl]amino-4-
          hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
          phenylmethyl-hexanamide;
                                                                    the personal property open
 25 (2R, 4S, 5S, 1'S, 1"RS) -5-((1"-(imidazol-2-yl)-2"-methyl)- es
          propyloxycarbonyl) amino-4-hydroxy-N-{1!-isopropyl-1!-
          imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide;
          (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'-
       isopropyl-1'-(4-(imidazol-2-yl)imidazol-2-yl)]methyl-6-
        phenyl-2-phenylmethyl-hexanamide; the Lyngham of the control of
         (2R, 4S, 5S, 1'S) -5-(1-oxo-thian-4-yl) oxycarbonyl) amino-4-
        hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
        phenylmethylhexanamide; or us and to the landquiet grade;
       (2R, 4S, 5S, 1'S) -5- ((tetrahydrosulfonylpyran-4- (1997))
35 yl) oxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-
        yl)methyl-6-phenyl-2-phenylmethylhexanamide; #b bersagssad
         (2R, 4S, 5S, 1'S) -5-((1, 1-dimethyl-2-(benzyloxycarb nyl-
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glycyloxy) ethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-

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imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-h xanamide
                               hydrochloride salt; y helphs the telester was received
                                        (2R, 4S, 5S, 1'S) -5-((1, 1-dimethyl-2-glycyloxy) ethoxycarbonyl) -
                            amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
             phenyl-2-phenylmethyl-hexanamidedihydrochloridesalt;
                  (2R, 4S, 5S, 1'S) -5- ((1-acetyl) amino-4-hydroxy-N-(1'-isopropyl-
                                      1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethylhexanamide;
                                       (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
  isopropyl-1!imidazol-2-yl)methyl-6-phenyl-2-(4-
                                     benzyloxyphenylmethyl) hexanamide; was a second and the second and
                  (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
     contracts isopropyl-1 imidazol-2-yl) methyl-6-phenyl-2-(4-
                   Figure hydroxyphenylmethyl) hexanamide; Figure 1 (19 1) and the figure
     (2R,4S,5S)-5-(t-butoxycarbonyl)amino-4-hydroxy-2-
                     15 phenylmethyl-6-phenyl-N-[1'-cyclopropyl-1'-imidazol-2-
             schiemyl]methyl-hexanamide; transfig- u-openhet - opening of
                - * 1) - r(2R, 4S, 5S, 1'S) -5- ((isopropylthiol) carbonyl) -amino-4-hydroxy-
     with the Arm 2-phenylmethyl-6-phenyl-N-[1-isopropyl-1'-imidazol-2-
    Tiveoxquiyl]methyl-hexanamide; ma iveman lokers it with by a
                                (2R, 4S, 5S, 1'S) -5-[3-(1H-imidazol-2-yl)-3-hydroxy-4-
               -- (1'-isopropyl-1'-imidazol-2-
    toblassim yl) methyl-6-phenyl-2-phenylmethyl-hexanamide; description
       (2R, 4S, 5S, 1'S) =5-[(4-methoxyphenoxy) carbonyl]amino-4-hydroxy-
                               N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
         25 phenylmethyl-hexanamide;
               - 1] -2R, 4S, 5S, 1'S) -5-(t-butylaminocarbonyl) amino-4-hydroxy-N-(1'-
                isopropyl-1;-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
                                    (2R, 4S, 5S, 1'S) -5- (methylaminocarbonyl) -; general unit
                   amino-4-hydroxy-N-(1:-isopropyl-1:-imidazol-2-yl)methyl-6-
    -S-30 to phenylmethyl-hexanamide; to block to the structure of the structu
                                  (2R, 4S, 5S, 1'S) -5-phenylaminocarbonyl) amino-4-hydroxy-N-(1'-
-S- (Aygonisopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide;
              (2R,4S,5S,1'S)-5-N-(propylaminocarbonyl)amino-4-hydroxy-N-
                                  (1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-
Hard 35 garhexamide; ) despressed to the form of the complex of the second of the complex of the
                  -3 - (2R, 4S, 5S, 1'S) -5- (n-propylaminothiono) amino-4-hydroxy-N-
                                  (1'isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide;
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2R, 4S, 5S, 1'S) -5- (isopropylaminocarbonyl) -amino-4-hydroxy-N-
                    (1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenylmethyl-
- (forespire hexamide; of the second of the second of the second of
    (2R, 4S, 5S, 1'S) -5- (aminocarbonyl) amino-4-hydroxy-N-(1'-
             5 isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide;
                    (2R, 4S, 5S, 1'S) -5- (6-quinolinylmethyloxy-carbonyl) amino-4-
    hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
         Phenylmethyl-hexanamide; The Market - 3- (att. 20 (24 )25)
                   (2R, 4S, 5S, 1'S) -5-(benzoyl) amino-4-hydroxy-N-(1'-isopropyl-1'-
                   imidazol-2-yl) methyl-6-phenylmethyl-hexanamide:
                (2R, 4S, 5S, 1'S) -5- (2-furylcarbonyl) amino-4-hydroxy-N- (1'-
                   isopropyl-1'-imidazol-2-yl) methyl-6-phenylmethyl-hexanamide;
                   (2R, 4S, 5S, 1'S) -5-(4-methoxybenzoyl) amino-4-hydroxy-N-(1'-
                   isopropyl-1'-imidazol-2-yl) methyl-6-phenylmethyl-hexanamide;
                   (2R, 4S, 5S, 1'S) -5-benzylcarbonyl) amino-4-hydroxy-N-(1'-11
                  isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide;
(2R, 4S, 5S, 1'S) -5- (4-hydroxybenzoyl) amino-4-hydroxy-N- (1'-
                  isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
                  (2R, 4S, 5S, 1'S) -5-(cinnamoyl) amino-4-hydroxy-N-(1'-isopropyl-
                  1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
                  (2R, 4S, 5S, 1'S) -5-(2-hydroxybenzoyl) amino-4-hydroxy-N-(1'-
                  isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
(2R, 4S, 5S, 1'S)-5-(imidazoyl-4-yl-acetyl) amino-4-hydroxy-N-
                  (1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-
                                                                         ter differencial finish in Committee
                 hexanamide:
                (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
             isopropyl-1'-(4-carbomethoxyethylimidazol-2-yl)]methyl-6-
                 phenyl-2-phenylmethyl-hexanamide; : : : (201, 2512 (41))
             (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
                 isopropyl-1'-(4-carboxamidoimidazol-2-yl)]methyl-6-phenyl-2-
    (i) phenylmethyl-hexanamide; (i) all the restriction of the second of th
            (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(5-(1-oxopropyl) -2-
                thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-
                yl))methyl-hexanamide;
                                                                       (x_0, \dots, x_{d+1}, \dots)
                 (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(5-(1-oxopropyl)-2-
                thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-
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the shore of y1)) methyl-hexanamide; she the for the firegoing the fit

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- ' : } - - - y(2R, 4S, 5S, 1, S) - 2-phenylmethyl-4-hydroxy-5-(5-propyl-2-
   - Lyr - Athiazolyl) amino) - 6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-
         yl))methyl-hexanamide; and
    (2R, 4S, 5S, 1'S) -5-(nicotinyl) amino-4-hydroxy-N-(1'-isopropyl-
   -5.5. (1'-imidazol-2-yl) methyl-6-phenylmethyl-hexamide.
              Another group of preferred representative compounds are:
- class [ ((2R,4S,5S,1'S)-5-[di(hydroxymethyl)-methoxycarbonyl]amino-4-
hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
         phenylmethyl-hexanamide; gives a according to a
   -- (10 -- (2R, 4S, 5S, 1'S) -5-(1, 1-dimethyl-2-acetoxyethoxycarbonyl) amino-
         4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
         phenylmethyl-hexanamide; has sumble was sone propagations
  -Percentum (2R, 4S, 5S, 1'S) -5-((1, 1-dimethyl-2-hydroxy) ethoxy-
  Sely recarbonyl) amino-4-hydroxy-N-(1.1-isopropyl-1.1-(4-) hage
         isopropylcarbonyl-imidazol-2-yl))methyl-6-phenyl-2-
 ndsdo Sephenylmethyl-hexanamide dihydrochloride salt;
       .e(2R,4S,5S,1'S)-5-((1S)-1-methyl-2-hydroxyethoxycarbonyl)-
   -phenyl-2-phenylmethylhexanamide; weekle of the literary
  20 (2R, 4S, 5S, 1'S) -5-((1R)-1-methyl-2-hydroxyethoxycarbonyl)-
  amino-4-hydroxy-N-(1!-isopropyl-1!-imidazol-2-yl)methyl-6-
    phenyl-2-phenylmethylhexanamide;
 as god or (2R, 4S, 5S, 1'S) 5- (1-hydroxymethyl-cyclopentyloxycarbonyl) -
       amino-4-hydroxy-N-(1 -isopropyl-1 -imidazol-2-yl) methyl-6-
 trad 25a phenyl-2-phenylmethyl-hexamide; of the tradition of the
     (2R, 4S, 5S, 18S) =5-(1, 1-dimethyl-2-hydroxyethoxycarbonyl) amino-
od Stansa4-hydroxy-N-(1!-isopropyl-1!-imidazol-2-yl)methyl-6-phenyl-2-
 Lives Liphenylmethyl-hexanamideDhydrochloride; 1990 with the
 .1721 (2R, 4S, 5S, 14S) -5- (hydroxyethoxycarbonyl) amino-4-hydroxy-N-
かつの30日本(1 = isopropyl-1 = -imidazol-2-yl) methyl-6-phenyl-2-
        phenylmethylhexanamide; and
ancher print(2R,4S,5S,1(S)-5-(2-hydroxy-1-methylethoxycarbonyl)amino-4-
Each hydroxy-N-(14-isopropyl-14-imidazol-2-yl)methyl-6-phenyl-2-
  The Long phenylmethylhexanamide darby a dark ments for the state of the
        (2R, 4S, 5S, 1; S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)-
 no remaino-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-
 chadechexanamid hydrochloride; dime a horsey and har how day
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(2R, 4S, 5S, 1'S) -5-(isopropoxycarbonyl) amino-4-hydroxy-N-(1'isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-phenylmethylhexanamide;

(2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-

- 5 isopropyl-1'-(4-isopropylcarbonyl-imidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide; games assistors
 - (2R, 4S, 5S, 1'S) -5-(1, 1-dimethyl-2-hydroxyethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide hydrochloride;
- 10 v (2R,4S,5S,1'S)-5-(hydroxyethoxycarbonyl) amino-4-hydroxy-N(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-i-phenylmethylhexanamide; and (2R,4S,5S,1'S)-5-(2-hydroxy-1-methylethoxycarbonyl) amino-4hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2phenylmethylhexanamide.

The term "alkyl" refers to a straight or branched chain alkyl radical of the indicated number of carbon atoms.

"C1-4alkyl" as applied herein is meant to include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl; "C1-6alkyl" includes additionally pentyl, isopentyl, 2-methylbutyl, 1-methylbutyl, 2-ethylpropyl; neopentyl, n-

- hexyl 2,2-dimethylbutyl, 2-methylpentyl, and the like.
 "Alkoxy" refers to an alkyl group of the indicated number of carbon atoms attached through a bridging oxygen atom.
- 25 "Alkylthio" refers to an alkyl group of the indicated number of carbon atoms attached through a bridging sulfur atom.

The term "substituted alkyl" as used herein is meant to include C₁₋₆alkyl, Ar-C₁₋₆alkyl, Het-C₁₋₆alkyl, C₂₋₆alkenyl, Ar-C₂₋₆alkenyl, Het-C₂₋₆ alkenyl, C₃₋₆cycloalkyl-C₁₋₆alkyl,

- 30 C3-6cycloalkenyl-C₁₋₆alkyl or C₁₋₆alkyl substituted with acyl or hydroxyl.
- "Alkenyl" refers to a straight or branched hydrocarbon chain of the indicated number of carbon atoms, which contains one or more carbon-carbon double bonds at any stable point
- 35 along the chain, such as ethenyl, propenyl, butenyl, from repentenyl, 2-methylpropenyl, hexenyl, and the like Hall
 - "Alkynyl" refers to a straight or branched hydrocarbon chain of the indicated number of carbon atoms which contains

, the gradual carbon-carbon triple, bond at any stable point along the control to the chain, such as ethynyl, 2-pr pynyl, 2-butynyl, 4-pentynyl, vigrammes 2-methyl-3-propynyl, hexynyl and the like. The control of The term "acyl" means R12-CO, wherein R12 is H, C₁₋₆alkyl, Ar-C₁₋₆alkyl, Het-C₁₋₆alkyl, C₂₋₆alkenyl, Ar-C2-6alkenyl, Het-C2-6alkenyl, C3-6cycloalkyl- C1-6alkyl, C5-6cycloalkenyl-C1-6alkyl, OH, NHR13, wherein R13 is H, Liver & OnC1-6alkyl, Ar-C1-6alkyl, Het-C1-6alkyl, C2-6alkenyl, Ar-C2-6alkenyl, Het-C2-6alkenyl, C3-6cycloakyl-C1-6alkyl, or Fig. 10:1 C3-6cycloalkyl, or C5-6cycloalkenyl-C1-6alkyl; or an α -amino Second or an α-amino alcohol bonded at the nitrogen. eligner in a cycloalkyl" refers to a saturated ring group of the indicated number of carbon atoms. "C3-7cycloalkyl" includes s miss sucyclopropyl, cyclobutyl, cyclopentyl, cyclobexyl and 15 "cycloheptyl" "Cycloalkenyl" refers to a saturated ring group of the indicated number of carbon atoms, having at least one contendocyclicocarbon-carbonodouble bond. "C5-7cycloalkenyl" we wincludes cyclopentenyl, cyclohexenyl and cycloheptenyl. "Aryl", abbreviated as Ar, refers to phenyl or naphthyl, optionally substituted with one to three halo, OH, OR10, C1-6alkyl, C1-6alkoxy, C1-6alkylthio, C1-6alkylamino, CF3, MED - CAREL amino, NO2, carboxy, C1-4alkylcarbonyl, aminocarbonyl, Hit field of C1-6alkyl-Het, C1-6alkoxy-Het, C1-6alkyl-phenyl, C1-6alkoxyone's phenyl, C1-6alkyl-, C1-6alkoxy-, HetC1-6alkyl-, HetC1-6alkoxy-, 25 phenylC1-6alkyl-, phenylC1-6alkoxy-for phenyloxy. areds . The entransmission herein except where noted, the term mheterocycle", abbreviated as "Het", represents a stable 5bibacd morto 7-membered monocyclic or a stable 7- to 10-membered was debbicyclic heterocyclic ring, which is either saturated or t of 300 unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, and o'O and S, and wherein the nitrogen and sulfur heteroatoms may hyperoptionally be oxidized, and the nitrogen heteroatom may see optionally be quaternized, and including any bicyclic group 35: in which any of the above-defined heterocyclic rings is fused -coto a benzene ring. The heterocyclic ring may be attached at Dust anytheteroatom; or carbon atom which results in the creation of as stable structure, and may optionally be substituted with

one to three halo, OH, alkyl, alkoxy; alkyl-Het, alkoxy-Het, alkyl-phenyl, alkoxy-phenyl... Examples of such heterocyclic elements include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, pyridyl, pyrazinyl, oxazolidinyl, oxazolinyl, oxazolyl, isoxazolyl, morpholinyl, thiazolidinyl, thiazolinyl, thiazolyl, quinuclidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzopyranýl, benzoxazolyl, furyl, pyranyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzoxazolyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl. Heteroaryl refers to a heterocycle which has aromatic character (eg., characterized by delocalized electron resonance and the ability to sustain a 15 ring current). Pyridine, imidazole, thiazole, furan and oxazole are examples of heteroaryl rings fact all the

"Amino acid" means the D- or L- isomer of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine or trifluoroalanine. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in Eur. J. Biochem., 158, 9 (1984). Usually lipophilic amino acids are preferred for the moiety B, for instance, Val, Ala, Leu and Ile. It will be understood that a linkage B-O refers to an oxygen atom bonded to the carboxyl group of an amino acid, and that a B-N linkage indicates a nitrogen atom bonded to the carboxyl group of an amino acid, as in an amide bond.

"Amino alcohol" refers to an amino acid in which the carboxyl group has been reduced to a methylene hydroxy group.

Certain chemical names are abbreviated herein for the sake of convenience. Boc refers to the t-butoxycarbonyl radical. Cbz refers to the carbobenzyloxy radical. Bzl refers to the benyzl radical. Ac refers to acetyl. Phorefers to phenyl. BOP refers to benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate. DCC refers to dicyclohexylcarbodiimide: DMAP refers to

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dimethylamin-opyridine. DMSO refers to dimethylsulfoxide. HOBT refers to 1-hydroxybenzotriazole. NMM is Nmethylmorpholine. DTT is dithiothreitol. EDTA is ethylenediamine tetraacetic acid. DIEA is diisopropyl ethylamine. DBU is 1.8 diazobicyclo[5.4.0]undec-7-ene. DMSO is dimethylsulfoxide. DMF is dimethyl formamide; Lawesson's reagent is 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4diphosphetane-2,4-disulfide and THF is tetrahydrofuran. refers to hydrofluoric acid and TFA refers to trifluoroacetic acid.

The compounds of formula (I):

The sequence of a contract of the second sec 15 wherein R4 is CO-NR CHR6R7, R5 is R10R11N-, and R1, R2, R3 and R6 are as defined in formula (I), are prepared by:

and well (a) coupling, a compound of the formula (II) : are red :

with a compound of formula (III):

od willsaorda vem adnoge will me HR'N-CHR6'R7' bar one transa

upon orthe there are mill, then and DMAR, which

where R1', R2', R3', R5', R6' and R7' are as defined for formula (I) with any reactive groups protected, Pr1 is H or a

hydroxyl protecting group, and L' is OH or a leaving group;

Bridge of Free Parketing bus (Linear (b) coupling a compound of the formula (IV):

with a compound of the formula (V):

or American the so their

on the strain and the strain of the strain o

wherein A' and B' are as defined in formula (I) with any reactive groups protected; or with some bound of the second of the seco

5 (c) coupling a compound of the formula (VI)

(VI)

with a compound of the formula (VII) the too well a

10

A'-L'

(VII)

and,

- 2) if appropriate, a coupling agent; and
- 3) removing any protecting groups and
- 15 4) forming a pharmaceutically acceptable salt thereof.

The coupling reactions may be accomplished by activating the substrate with a reactive functional group in situ or prior to the coupling reaction, such that it is reactive with an amino group. For instance, acids may be converted to acid chlorides, bromides, activated esters or anhydrides, or by adding a coupling reagent. Coupling agents are well known in the art for activating a functional group in situ,.

Exemplary of such agents are DCC and other carbodismides,
DMAPEC, BOP and PPA. These coupling agents may optionally be used with other reagents, such a HOBT, NMM and DMAP, which may facilitate the reaction.

Suitable leaving groups, L', are those which are displaceable by an amino group, such as bromo, chloro, a substituted acyl (eg. trifluoroacetyl, bromobenzoyl, nitrobenzoyl) or a substituted phenol (eg. 4-nitrophenol) and the like. If L' is OH, so that A-OH is an acid, it will be appropriate to use a coupling agent as hereinbefore described.

i 25 Julius is and do bepoment a distri

For instance:

vo beaucostog When A. is.a. substituted alkylagroup, such as To hold or R17 (R18R19C) m, 2L1; may be a bromo, chloro, iodo or an alkyl or Waryl'sulonate. Alb drive we do by the color of the

When Asis R17 (R18R19C) m-W, Ar-W or Het-W, and W is C=O, 5 on A-L' may be at carboxylic acid halide, activated ester or adanhydride, or accarboxylic acid in the presence of a coupling to fill agent. Methods for preparing such compounds are well known.

Act daily regard When: Wais OC=O, A-L' may be a chloro- or bromo-formate,

he contain activated carbonate. Haloformates may be prepared by

10 streacting the appropriate alcohol with phosgene or street carbonyldibromide. as Activated carbonates may be prepared by as goldreacting the appropriate calcohol with a suitable carbonate such as bis (4-nitrophenyl) carbonate. The house was a

24 35 Letting When Waise SO2 At A-L' may be a sulfonyl halide which may

W15 Webe prepared from the corresponding sulfonic acid.

which may be a chalothioformate, which may be prepared from a carbonyldihalide and an appropriate of a simercaptan. The boy of F windows of the control of the contr

and the first of the first of the second

Par May be a phosphonyl halide, 20 which may be prepared from the corresponding phosphonic acid. Compounds wherein A is R17 (R18R19C) m-W, Ar-W or Het-W,

and Wis NR C=O are ureas, and may be prepared by reacting a compound of formula (VII) with an isocyanate of the formula R¹⁷ (R¹⁸R¹⁹C)_m-NCO, Ar-NCO or Het-NCO, in a suitable solvent

such as methylene chloride, optionally with heating. - 25

Compounds of formula (III), wherein X is nitrogen, are imidazoles and may be prepared according to Scheme 1, wherein Pr2 is a removeable amino protecting group, and R7', R8' and R^{9} correspond to R^{7} , R^{8} and R^{9} as defined for formula (I), or 30 a group which may be converted into R7, R8 or R9, with any reactive groups protected.

no readel a ridia i a re Scheme 1

The amino aldehydes are generally known or are prepared by methods well known in the art, for instance, by reduction of a suitable α-amino acid ester with diisobutylaluminum hydride. Further reaction of the aldehyde with a gem 5 dialdehyde, or diketone, and ammonia yields the desired mail: imidazole. Alkylation and further modification of the wanth substituent groups of the imidazole area within the skill of the art. Such a method, and other methods for preparing imidazoles are disclosed, for instance, by Baldwin et al., J. Med. Chem., 29, 1065 (1986), Angewa Chem. Int., 22, 560 ! (1983); and Hughey et al., Synthesis, 1489d(1980) Alternately, acyl imidazoles may be prepared by coupling an α-amino acid to a substituted 4-amino-isoxazole, and subsequent reduction and base catalyzed rearrangement as disclosed generally by Reiter, L.A., J. Org. Chem., 52,2714 sing or all (1987). Intermediate compounds of formula (VIII) are a part of this invention. Preferably, R7 is C1-6alkyl and more preferably C3-6alkyl. Suitably, R8' and R9' are H, NO2, Br, COR^{12} , CF_3 , Ar, C_{1-6} alkyl or C_{1-6} alkyl- R^{15} , wherein R^{12} is H, 20 C₁₋₆alkyl, Ar, OC₁₋₆alkyl, NH₂, and R¹⁵ is OH or a protected

Compounds of formula (III), wherein X is sulfur, are thiazoles and may be prepared according to Scheme 2, wherein L' is a suitable displaceable group.

hydroxyl group. Preferably R9 is H or COR12. apply

25

Scheme 2 for single well.

of a stage in action engagines as done as

Accordingly, a thioamide is reacted with a ketone or aldehyde. Thioamides are commonly prepared from carboxamides by reacting the corresponding carboxamides with a reagent such as Lawessons reagent, as disclosed, for instance, by Hamada et al., Tet. Lett., 931 (1991). Suitable displaceable groups are those which are displaced by a sulfur nucleophile,

such as chloride, bromid , iodide, mesylate, p-tolunesufonate groups, and th like.

Compounds of formula (III), wherein X is oxygen, are oxazoles and may be prepared according to Scheme 3 from common amino acids.

The second of th

Typically the acid may be coupled to an appropriately 10 substituted amino alcohol by common techniques, as described -very above, and cyclized by treatment with thionylachloride to myield an oxazoline, as described by Meyers et al., J. Org. .inches Chem., 43, 1372 (1978). a Oxidation of the oxazoline, such as Top 15 cdescribed by Evans et al., J. Org. Chem., 44, 497 (1979),

The compounds of formula (II), (IV) and (VI), wherein R2 is H, are prepared, for instance, according to Scheme 4.

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Other methods for preparing protected 5-amino-4-hydroxy2,5-disubstituted-pentanoate esters and acids, and the corresponding \gamma-lactones, are well known and are disclosed, for instance, in Szelke et al., U.S. Patent 4,713,455, Boger et al., U.S. Patent 4,661,473, EP-A 0 352 000, Evans et al., J. Org. Chem., 50, 4615 (1985), Kempf, J. Org. Chem., 51,
10 3921 (1986), Fray et al., J. Org. Chem., 51, 4828 (1986), Halladay et al., Tett. Lett., 24, 4401 (1983), Wuts et al., J. Org. Chem., 53, 4503 (1988), DeCamp et al., Tett. Lett., 32,1867 (1991), and Szelke et al., WO 84/03044, all of which are incorporated herein by reference.

The compounds of formula (II), (IV) and (VI), wherein R² is OH, are also prepared by methods common in the art such as those disclosed in U.S. Patent 4,864,017; and Thaisrivongs et al., J. Med. Chem., 30, 976 (1987).

Compounds of formula (I), wherein R^5 is R^6-NR^{11} , are prepared according to Scheme 5, Scheme 6 or Scheme 7:

EB TO CONTROL BY STONE BY SCHEME 5

$$H_2N$$
 OPr^1
 R^3
 R^4
 R^4
 R^8
 R^8
 R^8
 R^8
 R^8
 R^8
 R^8
 R^8
 R^8

PARTY FORMARION TO AUSTRALIAN BY

Scheme 7

wherein R¹'-R⁴', R⁷' and R⁸' are as defined in formula (I) with any reactive groups protected, L' is a l aving group, 15 such as halogen, and Pr¹ is a hydroxy-protecting group and product of the product of

Compounds wherein R⁴ is R⁶NR¹¹— are prepared in an analogous manner from a compound of formula (IX):

Suitable protecting groups for the amino, hydroxyl, carboxylic acid, mercaptan group, and reagents for deprotecting these functional groups are disclosed in Greene et al., PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, Second 10 Edition, John Wiley and Sons, New York, 1991. Deprotection indicates the removal of the protecting group and replacement with an hydrogen atom. In particular, suitably substituted acetyl, benzyl and silyl groups are useful for protecting the hydroxyl group. The acetyl group is commonly removed by reacting the compound with a base, such as an alkali metal hydroxide, in a mixture of an alcohol and water. The silyl group, such as trimethyl silyl, dimethyl-t-butyl silyl, and t-butyl-diphenyl silyl may be removed by a fluoride reagent, such as a tetra-alkyl ammonium fluoride, or by acid The benzyl group may be removed by catalytic hydrolysis. hydrogenation.

Suitable protecting groups for the amino group are those disclosed by Greene et al., as indicated previously. The benzyloxycarbonyl and t-butoxycarbonyl groups are especially useful amino protecting groups.

The present invention includes pharmaceutically acceptable acid addition salts. Acid addition salts of the present compounds are prepared in a standard manner in a suitable solvent from the parent compound and an excess of an acid, such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, maleic, succinic or methanesulfonic. The acetate salt form is especially useful. If the final compound contains an acidic group, cationic salts may b prepared. Typically the parent compound is treated with an excess of an alkaline reagent, such as a hydroxide, carbonate or alkoxide, containing the appropriate cation. Cations such

cas Na+, &K+, Ca++ and NH4+ ar exampl s of cations present in pharmaceutically acceptable salts. Certain of the compounds 63-10.6 lformsinner salts or zwitterions which may also be acceptable. 53.5 0.5 M The compounds of the present invention selectively bind 50 to retroviral proteases in the same manner as the virally coded natural substrates of the proteases and compete with these substrates for protease, thereby serving to inhibit wiral replication by blocking the formation of crucial viral proteins from polyprotein precursors by the protease, and 10 hence, to inhibit disease progression in vivo. The present compounds achieve such beneficial therapeutic effect because they contain unique structural features which impart violate desirable pharmacokinetic properties to the compounds. such property is long duration of action. We have found that 15 substitution of a heterocycle, especially imidazole, in the putative P2 position of the present compounds affords compounds which retain good enzyme binding affinity, good antiviral activity, a favorable duration of action and water solubility for good drug delivery. A column to wanted a 20 When a compound of the present invention is administered

20 When a compound of the present invention is administered to an animal infected or potentially infected with a retrovirus, viral replication is inhibited and hence disease progression is retarded. Inasmuch as the amino acid sequences of the protease binding and peptide bond cleavage

- sites of various retroviruses appear to be highly conserved, an inhibitor is likely to be broadly active against more than one retrovirus. Also, DNA viruses which are dependant upon virally encoded proteases, such as the hepatitis virus, may also be susceptible to such treatment.
- The compounds of formula (I) are used to inhibit retroviral replication, and are useful in treating mammals, particularly human patients, who are infected with susceptible retroviruses and require such treatment. The method of treating a retroviral disease in a mammal,
- particularly a human, comprises internally administering (e.g. orally, parent rally, buccally, trans-dermally, rectally or by insufflation) to said mammal an effective amount of a compound of formula (I), preferably dispersed in

a pharmaceutical carrier. Dosage units of the active ingredient may be selected by procedures routine to one skilled in the art, and are generally in the range of 0.01-50 mg/kg. These dosage units may be administered one to ten times daily for acute or chronic infection. Preferably the compound is administered at a level of 1-10 mg/kg, two to four times daily. No unacceptable toxicological effects are indicated when compounds of this invention are administered in the above noted dosage range.

The present invention also provides a method of treating disease states associated with HIV infection or Acquired Immune Deficiency Syndrome (AIDS), comprising administering an effective amount of a compound of formula (I), preferably dispersed in a pharmaceutical carrier.

Beneficial effects may, be realized, by co-administering, individually or in combination, other anti-viral agents with the protease inhibiting compounds of the present invention. Examples of anti-viral agents include nucleoside analogues, phosphonoformate, rifabutin, ribaviran, phosphonothicate oligodeoxynucleotides, castanospermine, dextran sulfate, alpha interferon and ampligen. Nucleoside analogues, which include 2',3'-dideoxycytidine(ddC), 2',3'-dideoxyadenine(ddA) and 3'-azido-2',3'-dideoxythymide (AZT), are especially

useful. AZT is a preferred agent. Suitably, pharmaceutical compositions comprise an anti-viral agent, a protease inhibiting compound of the present invention, and a pharmaceutically acceptable carrier.

This invention is also a pharmaceutical formulation which comprises a compound of formula (I) and a pharmaceutically acceptable carrier. Pharmaceutical acceptable carrier are well known in the art and are disclosed, for instance, in SPROWL'S AMERICAN PHARMACY, Dittert, L. (ed.), J.B. Lippincott Co., Philadelphia, 1974, and REMINGTON'S PHARMACEUTICAL SCIENCES, Gennaro, A. (ed.), Mack Publishing Co., Easton, Pennsylvania, 1985.

Pharmaceutical compositions of the compounds of the present invention, or derivatives thereof, may be formulated as solutions or lyophilized powders for parenteral

administration. Powders may b reconstitut d by addition of a suitable diluent or other pharmac utically acceptable carrier prior to use. The liquid formulation is generally a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as ethanol, polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, these compounds may be encapsulated,

tableted or prepared in a emulsion or syrup for oral
administration. Pharmaceutically acceptable solid or liquid
carriers may be added to enhance or stabilize the
composition, or to facilitate preparation of the composition.

Liquid carriers include syrup, soy bean oil, peanut oil,
20 colive oil, glycerin, saline, ethanol, and water.

optionally with solubilizing excipients, are especially suitable. Oils include any natural or synthetic non-ionic water-immiscible liquid, or low melting solid, which is capable of dissolving lipophilic compounds. Natural oils, such as triglycerides are representative. In fact, another aspect of this invention is a pharmaceutical composition comprising a compound of formula (I) and an oil.

Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Solubilizing agents, such as dimethylsulfoxide or formamide, may also be added.

The carrier may also include a sustained release material assuch as glyceryl monostearate or glyceryl distearate, alone with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dedosage unit. The pharmaceutical pr parations are made

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following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is 5 used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule what a later than it

A suitable dosage form for oral administration has been prepared by dissolving the peptide of Example 1 (312.5 mg) in dimethyl sulfoxide (1:mL) and diluting to a concentration of 12.5 mg/mL with soybean oil. A suitable dosage form for intravenous administration has been prepared by dissolving the compound of Example 1 (0.02 g) in dimethyl sulfoxide (1 15 mL) and diluting to 20 mL with a 70% propylene glycol/30% blue is a ethanol solution. The services will be applied the many

For rectal administration, a pulverized powder of the compounds of this invention may be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository. Another pulverized a powders may also be compounded with an oily preparation, gel, cream or emulsion, buffered or unbuffered, and administered through a transdermal patch. Language and Linguistics

The pharmacological activity of the compounds of this 25 dinvention may be demonstrated by enzyme assays to determine the inhibitory activity of the retroviral protease, by in vitro cellular-based assays to determine the ability of the compounds to penetrate cells and inhibit viral replication, and by pharmacokinetic assays to determine oral 30 bioavailability, drug half-life and clearance. These assays are well known in the art. A way are an an ortist with

ENZYME ACTIVITY TO THE RELEASE THE SECOND TH

The ability of the compounds of this invention to inhibit the HIV-1 protease enzym may be demonstrated by using the assay disclosed by Dr yer et al., Proc. Natl. Acad. Sci., U.S.A., 86, 9752 (1989), Grant et al., Biochemistry, 30 8441 (1992), and EP-A 352 000. The K_i for the compounds of

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this invention are in the range of 1 nM to 5 µM. Preferred
               compounds, have Ki's of less than 100 nM.
                                                                                                     The Beginner
     boloca) Chaf. 0-30 emilion larger a sel datagram, gape acatampos
       The ginfectivity of hear this year (Circle wild less i seaon)
         2.5. Complete The ability of the compounds of this invention to gain
    entry to cells infected with the human immunodeficiency
         equiviewirus, and to inhibit viral replication in vitro may be
     dm 6.0 demonstrated using the assay described by Meek et al.,
    secus & Nature, 3343, 590 (1990), and Petteway et al., Trends
of blode Pharmacol. Sci, 12, 28: (1991) and The IC50 for the compounds of
          this invention are in the range of 0.1 to 10 µM.
    course it a felle of the city ob of the estracted scaple was
        Em 4 CYTOTOXICITYS ALl pageto new with a right of the factor
    Remark to Reference Cytoitoxicity is assessed by both direct microscopic
         15 examination of trypan blue stained cells (T-lymphocytes) and
  yd fod: by the treated culture stability to metabolize the
          Amendetrazolium@salteXTT- (2,3-bis[2-methoxy-4-nitro-5-to-
no drawn sulfophenyl]-2H-tetrazolium-5-carboxanilide:sodium salt), to
        {\tt mod}^*({\tt its}) formazan, {\tt dye}\,\lambda_{J} . The <code>:XTT_assay_sallows determination of the</code>
        20 50% toxic concentration of compounds for the cell/virus a
add lo ([system used.car] . Magra Grindelship socon a situati)
    and the property of the tip of the complete of the property and the complete of the complete o
    BOLDER PHARMACOKINETICS: EDEMON to COAD, CLOSE WAY TO BE DESCRIPTION.
  : Boldpape em.Dualbjugular:cannulated Sprague Dawleysrats:weighing 200
                to 250 g were utilized in all studies. All dosing and sample
    con ex (collection was) done from conscious rats. Before dosing, a
  actions of time: O.blood sample, #300 ppl, was drawn using one of the
              catheters. Utilizing the second catheter the rats were dosed
 # Love L (intravenously at 1,610, 30, 60, 90, 120, 150, 180 and 210 ...
bed: 30 a min, after dosing, 300 µL blood samples, were drawn. To The rats
To notethedosed@orally weregadministered the compound by utilizing a 22
   All of gauges gastric gavage needle and samples were drawn sat 30, 60,
 of anima0, 120, 3240, 360, 480, 600, 720 and 1440 min. The blood
        samples were placed-in precooled tubes containing 30 mL of
       35g sodium citrate and centrifuged in a microfuge of The plasma
 was was transferr d then snap frozen on dry ice, and stored at
 edd the a70°C until analyzed. His aminopher (who he is to be lived
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rectanged to appear to the distance of the distance of the mathematical

Standard stock solutions (1 mg/mL) of inhibitor was prepared in 100% DMSO. A dilution series of the stock solutions were prepared in a total volume of 0.1 mL (pooled normal rat plasma/DMSO) to yield final concentrations of 0 and 0.5-120X the Ki of the inhibitor All dilutions were performed in triplicate. These spiked plasma solutions were extracted with 0.5 mL acetonitrile by vigorous vortexing. followed by centrifugation for 10 min. An aliquot (0.4 mL) of the supernatant was removed and dried in Eppendorf tubes 10 di 10 dusing a Speed-vac. The resulting residue was redissolved in DMSO. The inhibition of the HIV-laprotease activity was assayed as follows. An aliquot of the extracted sample was added to a 50 µL mixture containing 1X MENDT buffer 1 mM substrate and incubated at 37°C < 10 min of The reaction was han 15 then initiated by the addition of HIV-1 protease and continued at 37°C for an additional 15 min athen quenched by the addition of TFA (0.5% final concentration) TexInitial or a contract were determined for each standard curve as the fraction of to coffremaining enzymatic activity (vi/v0) at each inhibitor 20 concentration, in which vo is the velocity of the To (inhibitor concentration)=0 sample. Assuming that all of the original inhibitor in the spiked samples was extracted, the values of vi/vo were plotted versus inhibitor concentration 991 palagofathe original extracted sample and fitted to the equation: 5 m 25 m vi/vo=[AEt - It - Kis+s (Ki-AEt-It) 0.5]/(2AEt), p. (6.2 cm) # And in which Et is the total enzyme concentration at time zero, Ki is the apparent inhibition constant and A is the fraction the witer of active enzyme. The one can painfield and design as Ex vivo animal plasma samples containing unknown levels of protease inhibitor were prepared and analyzed as described 5 B D for the standard curve described above . The concentration of inhibitor in these samples was then determined using the Ki and A parameters from the fitted standard curve according to the following equation: $c I_t = A E_t [1 - (v_i / v_0)] + K_i (v_0 / v_i)$. " 350 of The data was plotted as the natural log (ln) of the plasma concentration versus time on semilogarithmic paper to generate the plasma concentration-vs-time curves. Using the IV data, the apparent terminal rate constant was determined

concentration-vs-time curve. The elimination half-life (t1/2) was derived by dividing ln 0.5 (=0.693) by the terminal rate constant. The area under the plasma

5 concentration-vs-time curve (AUC) was determined by using the ln/log trapezoidal rule. Cmax represents the maximal plasma concentration and tmax, the time following drug administration at which Cmax was observed. Both values were estimated by inspection of the plasma concentration-vs-time curve. Total plasma clearance (CL) was calculated by dividing the dose by the AUC. The fraction of the oral dose fraction, F) was determined by the equation: F =

[AUCpo/DOSEpo] xx[DOSEiv/AUCiv].

The Examples which follow serve to illustrate this best printed to limit the scope of this invention, but are provided to show how to make and use the compounds of this invention.

Centigrade. Mass spectra were performed using fast atom bombardment (FAB) or electro-spray (ES) ionization. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

NMR were recorded at 250 MHz using a Bruker AM 250 (000) spectrometer, unless otherwise indicated. Chemical shifts are reported in ppm((δ)) downfield from tetramethylsilane.

Multiplicities for NMR spectra are indicated as: s=singlet, dd=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets, dt=doublet of triplets etc. and br indicates a broad signal. J indicates the NMR coupling constant in Hertz.

Celite® is filter aid composed of acid washed
diatomaceous silica manufactured by Mansville Corp., Denver,
Cov 35. Colorado. Florisil® is an activated magnesium silicate
chromatographic support and is a registered trademark of
Floridon Co., Pittsburgh, Pennsylvania. Sat. indicates a

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saturated solution, eq indicates the proportion of a molar equivalent of reagent relative to the principal reactant.

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Preparation of (2R,4S,5S,1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)amino-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide hydrochloride)

10 a) (1'S)-1'-carbobenzyloxyamino-1'-isopropyl-1'-(imidazo-2-

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Cbz-valinal (4.6 g, 1 eq) and glyoxal trimeric dihydrate (1.33 g, leq) were stirred in MeOH at -10°C. Ammonia was bubbled through the solution for several min and the mixture was allowed to stir for 4 h at -10°C. The mixture was allowed to warm to room temperature over 14 h, then was poured into 250 mL water. The suspension was filtered and the filter cake washed twice with water to give the title compound as a white solid (1.9 g, 36%). NMR(CD3OD) & 7.28

20 (5H, m), 6.89 (2H, s), 5.04 (2H, dd), 4.46 (1H, d), 2.10 (1H, m), 0.91 (3H, d), 0.70 (3H, d); MS(CI/CH₄) m/e 274.2 [M+H]⁺, 230.1, 166.1, 123.1, 91.1.

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- b) (1'S)-1'-amino-1'-isopropyl-1'-(imidazo-2-y1) methane
 25 (1'S)-1'-carbobenzyloxyamino-1'-isopropyl-1'-(imidazo-2-y1) methane (1.9 g) was stirred in methanol over 10% Pd/C (200 mg). Hydrogen was bubbled through the solution for 1 h and the solution was maintained under a positive hydrogen atmosphere overnight. The mixture was filtered through
 30 Celite® and was evaporated to a tacky solid (720 mg, 75%). NMR (CDC13) δ 6.87 (2H, s), 3.88 (1H, d), 2.04 (1H, m), 0.81 (6H, dd); MS (DCI/NH3) m/e 190.2 [M+H]+.
 - c) (2R,4S,5S,1'S)-2-phenylmethyl-4-(t-butyldimethyl)siloxy-5-35 (t-butoxycarbonyl)amino-6-phenyl-N-[1'-isopropyl-1'-(imidazo-2-yl)]methyl-hexanamide

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To a solution of (2R, 4S, 5S)-2-phenylmethyl-4-(t-butylmethyl) siloxy-5-(t-butoxycarbonyl) amino-6-phenyl-

hexanoic acid (200 mg, 0.38 mmol) in dichloromethan , (1'S)too i p li-amino-li-isopropyl-1'-(imidazo-2-yl)methane (48 mg, 0.35 . element mmol), BOP reagent (168 mg, 0.38 mmol), and triethylamine statement of (0.053 mL, 0.38 mmol), were added. The mixture was stirred company 5 mounders argon overnight, and washed successively with water, 5% hedane, waqueous, sodium bicarbonate; and saturated aqueous sodium op. 5 % chloride. The solution was dried over MgSO4, filtered, and The solid was chromatographed (silica, 4% methanol/dichloromethane) to afford the title 10 compound as a white solid (0.154 g, 68%). NMR(CDCl₃) δ 7.18 (10H, m), 6.91 (2H, d), 6.32 (1H, d), 4.69 (1H, d), 4.40 (1H, moone due t); 3.92 (1H, eq), 3.63 (1H, m), 2.84 - 2.31 (6H, m), 1.67 (6H, 6.5) (4H, 1m), 1.24((9H, s), 0.89 (9H, s), 0.74 (6H, dd), 0.05 (6H, $\text{MeV}_{\text{total}} = \text{d}$; MS(DCI/NH₃) m/e 649.6 [M+H]+. . ter . S 15 militer in de mayor mondo é alt es odo se la reconstit

The compound of Example 1(c) (0.140 g) was stirred in 20 THF at room temperature under an argon atmosphere.

Tetrabutyl ammonium fluoride (0.38 mL, 6 eq) was added and the solution was stirred overnight. The mixture was diluted with water and extracted with dichloromethane (3X). The combined organic extracts were washed with water and extracts were washed with 1 eq of methanolic extracts was treated with 1 eq of methanolic extracts was treated with diethyl ether and extracted, and triturated with diethyl ether and extracted to give the title compound as a white solid (95 mg, 83%). NMR (DMSO-d6) & 7.78 (1H, d), 7.16 (10H, m), 6.71 (2H, s), 6.39 (1H, d), 4.68 (1H, m), 4.52 (1H, d), 2.71 (3H, d), 2.48 (3H, m), 1.97 (1H, m), 1.61 (1H, m), 1.30 (9H, s),

 $0.78 (3H, d)_{12} 0.61 (3H, d)_{12} MS (DCI/NH₃) m/e 535.4 [M+H]+...$

dest amenos all applie and the first of Example 2

Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(t
Book butoxycarbonyl) amino-6-phenyl-N-[1'-isopropyl-1'-(4
aminocarbonyl-thiazo-2-yl) lmethyl-hexanamide

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To a solution of di-t-butyl-dicarbonate (7:15 g, 1 eg) in dry dichloromethane was added valinamide hydrochloride (5.0 g, 1 eq) and triethylamine (9.14 mL, 2 eq) . The mixture 5 was heated to reflux for 4 h, and cooled to room temperature. The organic layer was washed twice with water and evaporated to give the title compound (6.03 g, 85%). NMR(CDCl₃) δ 6.00 3393 (1H, br), 5.54 (1H, br), 5.01 (1H, br), 3.93 (1H, dd), 2.12 (1H, m), 1.44 (9H, s), 0.92 (6H, dd) . 61 (15 (54)) t in the state of compound as a chica no.

b) Boc-valinethioamide [hour (if (ani) 14.3) (ex \((ax \) (0.1) \)

Boc-valineamide (0.5 g) was stirred in dry THF at room temperature under argon. Lawesson's reagent ((1.56) q, 0.6 eq) was added and the mixture was stirred overnight. The solvent was evaporated and the residue chromatographed (silica, 2.5% methanol/dichloromethane) to give the title compound as a white solid (0.373 g; 70%) $\sim NMR(CDCl_3) \pm \delta \approx 8.59 \pm (1H_H br s)$, 8.09 (1H, br s), 5.41 (1H, d (br)), 4.20 (1H, dd), 1.99 (1H, . ab a Am), 1.39 (9H, s), 0.90 (6H, m). a 首の 電影 (4) (4) (4)

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Mark Dac) (1'S)-1'-(t-butoxycarbonyl)amino-1!-isopropyl-1!-(4bear the carboethoxythiazo-2-yl) methane with each good before each

Boc-valinethioamide (0.265 g) was stirred in dry acetone under argon at -10°C. Ethylbromopyruvate (0.16 mL, 1.1 eq) 25 was added and stirred for 1 heat -10°C. The solution was poured into a well-stirred mixture of chloroform and water ger Gran and then saturated with sodium bicarbonate. The organic phase was separated and the aqueous layer extracted with chloroform. The combined organic extracts were dried over 30 MgSO₄, filtered, and evaporated to an oil; The oily residue was treated with trifluoroacetic anhydride (0.16 g) and pyridine (0.2 g) in dichloromethane for 1 h at -20°C. Excess solvent was removed in vacuo and the residue dissolved in dichloromethane. The solution was washed with sat. aqueous 35 sodium bicarbonate and 1.0N KHSO4 until pH 7. The solution was dried over sodium sulfate, filtered, and evaporated to an oil which was chromatographed (silica, 4% methanol/ dichloromethane) to give the title compound as a tan solid.

(1H, m), 5.35 NMR (CDCl₃): δ 8.04 (1H; s), 5.26 (1H; brid), 4.85 (1H, m), 5.36 (1H, m), 6.36 (2H, πq); 2.405 (1H, m), 1.41 (9H, s), 1.34 (3H, t), 0.93 (3H, d), 0.84 (3H, d). (3H, d). (3H, d).

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5 d) (1'S)-1'-(t-butoxycarbonyl)amino-1'-isopropyl-1'-(4-

The compound of Example 2(c) (50 mg) was stirred in THF at 0°C. Excess 1.0N NaOH was added and the mixture was stirred for 12 h at 0°C. The mixture was diluted with 1.0N

citric acid and extracted with dichloromethane (3X). The combined organic extracts were evaporated and dried in vacuo to give the title compound (0.045 g, 98%). NMR(CDCl₃) δ 8.08

O3 (1H, s), 5.19 (1H, m), 4.80 (1H, m), 2.31 (1H, m), 1.38 (9H, 88.7 8 s), 0.86 (6H, dd).

(a) (1'S)-1'-(t-butoxycarbonyl) amino-1'-isopropyl-1'(4-aminocarbonylthiazo-2-yl) methane

(1'S)-1'-(t-butoxycarbonyl)amino-1'-isopropyl-1'-(4-carboxythiazo-2-yl)methane (0.078 g, 0.26 mmol) was stirred under argon in dry THF at -40°C. NMM (0.06 mL; 0.55 mM) and isobutyl chloroformate (0.034 mL; 0.26 mmol) were added. After stirring 15 min, ammonia was bubbled through the mixture for several min. The solution was warmed to room

termperature and the THF evaporated. The residue was diluted with ethyl acetate and washed successively with 1.0N citric as as acid, 5% aqueous sodium bicarbonate, and sat. aqueous sodium bicarbonate, and sat.

and evaporated to a solid which was chromatographed (silica, 3% methanol/dichloromethane) to give the title compound as a white solid (0.052 g, 67%). NMR(CDCl3) 8 8.02 (1H, s), 7.14 (1H, ms(br), 6.28 (1H, s(br)), 5.24 (1H, d(br)), 4.82 (1H, m), 1.39 (9H, s), 0.92 (6H, dd).

(2R, 4S, 5S, 1'S) -2-phenylmethyl-4-(t-butyldimethylsiloxy)-5-35-(t-butoxy carbonyl)amino-6-phenyl-N-[1'-isopropyl-1'-(4-aminocarbonyl-thiazo-2-yl)]methyl-hexanamide

(14) (1.5) (58 (1.6)) 5.06 (1.0) 68 (1.5) (1.4)

The compound of Example 2(e) (52 mg) was stirred in neat trifluoroacetic acid for 10 min and evaporated. The residue

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was diluted with methanol and tr at d with 2 eq. of conc. HCl. The solvents were evaporated and dried in vacuo to give a white solid. This solid (40 mg) was added to a solution of (2R, 4S, 5S) -2-phenylmethyl-4-(t-butyldimethyl) siloxy-5-(tbutoxycarbonyl) amino-6-phenyl-hexanoic acid (97 mg, 1.1 eq),

DCC (38 mg, 1.1 eq), and HOBT = (0.05 g, 2.2 eq) in DMF at room THE RELEASE temperature under argon. N-methylmorpholine (0.04 mL; 2.2 eq) was added and the mixture was stirred overnight. mixture was filtered through Celite®, evaporated, and diluted with ethyl acetate. The solution was washed successively with 1.0N citric acid, 5% aqueous sodium bicarbonate, and (1) 8 7 - 1 sat. aqueous sodium chloride and The organic layer was chromatographed (silica, 2.5% methanol/dichloromethane) to

(1H, s), 7.60 (1H, d), 7.24 (10H, m), 6.82 (1H, m), 5.12 (1H, m), 4.89 (1H, m), 3.92 (1H, q), 3.81 (1H, dd), 2.73 (4H, m), 2.21 (1H, m), 1.73 (2H, m), 1.40 (9H, s), 1.23 (1H, m), 0.93 (9H, s), 0.84、(6H, dd), 0.11、(6H, d), 20(1)

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yield the title compound (60 mg, 55%). NMR (CDCl3) δ 7.89

20 g) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-) butoxycarbonyl) amino-6-phenyl-N-[1'-isopropyl-1'-(4aminocarbonyl (thiazo-2-yl)] methyl-hexanamide

The compound of Example 2(f) (60 mg) was stirred in dry THE under argon and tetrabutylammonium fluoride (0.50 mL, 6 25 eq) was added. The solution was stirred at room temperature with water, the aqueous layer was Absolute extracted with dichloromethanes (3X) a The combined organic extracts were washed with water, evaporated, and triturated with diethyl ether and ethyl acetate to give a tan solid.

 $\pi_{ij} \approx 30$. The solid was chromatographed (silicargel) 14% $\pi_{ij} \approx p + q \pi$ methanol/dichloromethane) to give the title compound as a white solid (0.022 g). NMR(CDCl₃) δ 7.90 (1H, s), 7.15 (10H, m), 6.39 (1H, d), 5.93 (1H, br s), 5.06 (1H, dd), 4.91 (1H, d), 3.90 (1H, d), 3.67 (2H, m), 2.91 (4H ρ m), 2.64 (1H, d),

35 2.13(1H, m), 1.87 (3H, m), 1.36 (9H, s), 0.83 (6H, dd); $MS(DCI/NH_3)$ m/e 612 [M+NH₄]⁺, 595 [M+H]⁺, 495, 413.1, 391, 374, 356, 239.1, 202, 185.

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The compound of Example 2(c) was stirred in neat quinoline. Cu powder (0.50 g) was added and the suspension was heated to 160°C for 2 h. After cooling to room temperature, the solution was diluted with ethyl acetate and washed with 2.0N citric acid (4X). The organic layers were combined and dried over MgSO4, filtered, and evaporated to a 15 mdark oil. The oil was chromatographed (silica, 4%

boundies methanol/dichloromethane) to give the title compound as an any (Alorange oil, 132 NMR (CDCl3) (δ.7.68 (1H, d), 7.19 (1H, d), 5.26 (1H, d), 4.88 (1H, m), 2.31 (1H, m), 1.43 (9H, s), 0.92 (3H, (1H, d), 0.84 (3H, d).

b) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t
9Assides (butoxycarbonyl) amino-6-phenyl-N-[1'-isopropyl-1'-(thiazo-2cle banyl)]methyl-hexanamide)

(DMSO-d6) & 8.31 (1H, d), 7.62 (1H, d), 7.49 (1H, d), 7.16

-8A 7 6 ((10H,0)m)%, 2.61 (6H, m), 1.28 (9H, s), 0.89 (3H, dd); 30 MS (DCI/NH3) m/e 552.3 [M+H]+, 413.2, 331.1, 183.1, 157.1, 142.0, 120.138 S.Ost Ma (288.138.138.138.138.1)

t Beyrofile (Byd Legibal y 2004 or - 1 - Angoda) - **Example 4** (1997) - 1995 style (1

35 Preparation of (2R,4S,5S,1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)amino-6-phenyl-N-(1'-isopropyl-1'-benzimidazo-ligg 2-yl) | methyl-hexanamide --b)-4 www.[2b(-yz) -- benzimidazo-

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a) (1'S)-1'-carbobenzyloxyamino-1'-isopropyl-1'-(benzimidazo-2-yl) methane

Cbz-valine (2.0 g, 1 eq) was stirred at -10°C in dry THF under argon. Triethylamine (1.11 mL, 1.0 eq) was added, followed by isobutyl chloroformate (1:03 mL, 10ed) The reaction mixture was stirred for 10 min. Phenylene diamine constitution (0.944 g, 1.1 eq) was added slowly cin 10 ml/dry THF. The mixture was warmed to room temperature and stirred for 1 h. The solvents were evaporated and the residue partitioned 10 between water and ethyl acetate. The ethyl acetate laver was washed with 5% aqueous sodium bicarbonate and brine. but the organic layer was dried over MgSO4, filtered, and evaporated. STAR The residue was dissolved in glacial acetic acid and heated to 65°C for 16 h. The solvents were evaporated and the residue diluted with water. After neutralizing with at The the saturated aqueous sodium bicarbonate, the solid was filtered and the filter cake was washed with hexane. The solid was $(\mathcal{E}_{i,j})$ age g recrystallized from ethylgacetate and hexane. NMR(CD3OD) δ 7.48-7.11 (9H, m), 5.06 (2H, q), 4.62 (1H, m), 2.27 (1H, m), 1.23 (1H, m), 1.02 (3H, d), 0.84 (3H, d).

b) (1'S)-1'-amino-1'-isopropyl-1'-(benzimidazo-2-yl) methane The compound of Example 4(a): (2.76 g) was stirred in methanol. 10% palladium on activated carbon (Pd/C) (250 mg) 25 was added and hydrogen gas was bubbled through the solution for 1 h. The reaction was maintained under an hydrogen atmosphere overnight. The mixture was filtered through Celite® and the solvents evaporated to give the title compound as a white solid (1.58 g, 98%). NMR (CDC13) 8 7.48-30 7.10 (4H, m), 4.02 (1H, d), 2.24 (1H, m), 0.96 (3H, d) 0.83 (3H, d); MS(DCI/NH3) m/e 190.2 [M+H] + all to the

c) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-(t-butyldimethyl) siloxy-5-(t-butoxycarbonyl)amino-6-phenyl-N-[1'-isopropyl-1'benzimidazo-2-yl]methyl-hexanamide in to note the year at

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To a solution of (2R, 4S, 5S) -2-phenylmethyl-4-(tbutyldimethyl) siloxy-5-(t-butoxycarbonyl) amino-6-phenylhexanoic acid (75 mg, 1.1 eq) in dimethyl formamide under

- argon, the compound of Exampl 4(b) (25 mg, 1.0 eq), DCC (30 mg, 1.1 eq) and HOBT (44 mg, 2.2 eq) were added. The mixture was stirred overnight, then filtered through Celite®. The solvents were evaporated and the residue was
- 5 chromatographed (silica gel, 4% methanol/dichloromethane) to give the title compound (0.070 g, 78%). NMR(CDCl₃) δ 7.88 (1H, d), 7.30 (14H, m), 6.80 (1H, d), 4.93 (2H, m), 4.26 (1H, q), 4.00 (1H, m), 2.92 (7H, m), 2.01 (2H, m), 1.53 (9H, s), 1.20 (9H, s), 1.14 (6H, d), 0.41 (6H, d); MS(DCI/NH₃) m/e 10 699.6 [M+H]+.
- (ETM (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl) amino-6-phenyl-N-[1'-isopropyl-1'-benzimidazo-2-yl]methyl-hexanamide
- The compound of Example 4(c) was stirred in dry THF and tetrabutyl ammonium flouride (0.6 mL, 6 eq) was added. The mixture was stirred under argon overnight at room temperature. The solution was diluted with water and extracted with dichloromethane (3X). The combined organic layers were washed with water and evaporated to a residue which was chromatographed (silica, 2% methanol/CH₂CL₂) to give the title compound (0.029 g, 50%). NMR(CDCl₃) & 7.54 (1H, m), (7.11 (11H, m), 6.69 (4H, s), 4.98 (1H, d), 4.69 (2H, m), 3.66 (2H, m), 2.74 (5H, m), 2.31 (1H, m), 1.73 (2H, m), 1.32 (9H, s), 0.70 (6H, d); MS(DCI/NH₃) m/e 585.4 [M+H]⁺, das 413.3, 364.3, 296.2, 190.2, 173.1, 120.1.

Example 5

- 30 Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)amino-6-phenyl-N-(1'-imidazo-2-yl)methyl-hexanamide hydrochloride

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substituting Cbz-glycinal for Cbz-valinal, the title compound was prepared. NMR (CDCl₃) δ .33 (5H, s), 6.95 (2H, s), 5.95

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(1H, s(br)), 5.12 (2H, s), 4.42 (2H, d); MS(DCI/NH3) m/e 232.2 [M+H]+, 188, 171.

b) (2R,4S,5S,1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl) amino-6-phenyl-N-(1'-imidazo-2-yl) methyl-hexanamide hydrochloride

Following the procedure of Example 1(b)-1(d), except substituting the compound of Example 5(a) for (1'S)-1'-carbobenzyloxyamino-1'-isopropyl-1'-(imidazo-2-yl)methane, the title compound was prepared. NMR(CD3OD) & 7.20 (10H,m), 6.94 (2H,s), 6.11 (1H,d), 4.24 (2H,dd), 3.61 (1H,m), 3.52 (1H,m), 2.69 (4H,m), 1.66 (2H,m), 1.28 (9H,s); MS (DCI/NH3) m/e 493.7 [M+H]+, 475.7, 120.2, 98.2, 83.1, 69.1.

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Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)amino-6-phenyl-N-[1'-methyl-1'-(imidazo-2-yl)]
methyl-hexanamide hydrochloride

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a) (1'S)-1'-carbobenzyloxyamino-1'-methyl-1'-(imidazo-2-yl)methane

Following the procedure of Example 1(a), except substituting Cbz-alanal for Cbz-valinal, the title compound was prepared. NMR(CDCl₃) δ .35 (5H,s), 6.92 (2H,s), 5.52(1H,d), 5.12 (2H,q), 4.90 (1H,q); MS(DCl/NH₃) m/e 246 [M+H]⁺, 202, 185.

b) (2R, 4S, 5S, 1'S)-2-phenylmethyl-4-hydroxy-5-(t
butoxycarbonyl) amino-6-phenyl-N-[1'-methyl-1'-(imidazo-2-yl)]

methyl-hexanamide hydrochloride

Following the procedure of Example 1(b)-1(d), except substituting the compound of Example 6(a) for (1'S)-1'-carbobenzyloxyamino-1'-isopropyl-1'-(imidazo-2-yl)methane, the title compound was prepared. NMR(CD₃OD) δ 7.11(10H, m), 6.86 (2H, s), 4.69 (1H, d), 3.62 (1H, d), 3.51 (1H, m), 2.68 (6H, m), 1.59 (2H, m), 1.30 (9H, s), 1.14 (3H, d); MS(DCI/NH₃) m/e 507.5 [M+H]⁺, 489.4, 112.1.

THE CONTRACTOR OF THE STANDARD BOARD CONTRACTOR OF THE CONTRACTOR ende sou pad bigg . Dede togeth go tops Example 7 Togethe or transmit the edge by early the afford the title indungation of (c) - 0 Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(t-Salf 5(m butoxycarbonyl)amino-6-phenyl-N-[1'-benzyl-1'-(imidazo-2-.Bif) 38.2 vl) | methyl-hexanamide hydrochloride | max 2016 | 2017 10 min 30 m 1 m 1 m a) (1'S)-1'-carbobenzyloxyamino-1'-benzyl-1'-(imidazo-2yl)methane - ALA ME 58 Following the procedure of Example 1(a), except who was substituting Cbz-phenylalaninal for Cbz-valinal, the title compound was prepared. NMR(CDCl₃) δ 7.37-7.05 (10H,m), 6.95 (2H, s br), 65.526 (1H, d), 5.050 (2M, s), 4.950 (1H, q), 3.32 (2H, d); MS(DCI/NH₃) m/e 322, 261, 171. m and miningon, minimorphic and government and a que b) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t- 2) butoxycarbonyl)amino-6-phenyl-N-(1'-benzyl-1'-(imidazo-2-yl)) ाहार बंध Following the procedure of Example 1 (a) -1 (d) , except 20 substituting the compound of Example 7(a) for (1'S)-1'carbobenzyloxyamino-1!-isopropyl-1!-(imidazo-2-yl)methane, the title compound was prepared. NMR (CD3OD) δ 7.15 (15H, m), 1001 286 6.79 (2H, 18), 65%78 (1H, td), 5:04% (1H, d), 3.58 (1H, m), 3.47 THE O. RED. (1H, EM), \$20.68% (8H, EM), 1059% (2H, EM), 1031% (9H, ES). Mary 25th aland the depaid through plaint add to (2007) whatle bilingua et a gonodisonancia de Example 8 para es desile i beli ling builded and the believe we a Side of Preparation of (2R.4S.5S.1'S)-5-(carbobenzyloxy) amino-4-6 (10) hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-

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10.2 300 phenylmethyl-hexanamide ... Or . MS. Do & ... (m. 1222) a.

was poured into H₂O and extracted with dichloromethane. The combined organic extracts were evaporated, and the residue was triturated with diethyl ether to afford the title compound as a white solid. NMR(CD3OD) δ.7.36-6.94 (15H, m), 5 6.84 (2H, s), 4.99 (2H, s), 4.54 (2H, d) pc3.76 (1H, m), 3.52 (1H, dd), 2.77 (5H, m), 2.04 (1H, m), 21.76 (1H, m), 1.58 (1H, m), 0.82 (3H, d), 0.66 (3H, d).

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Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4.5-dimethyl)imidazol-2yllmethyl-6-phenyl-2-phenylmethyl-hexanamide(50.005)

a) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(4,5-dimethylimidazol-2-yl)methane

butanedione (1.54 mL, 1.0 eq). Ammonia was bubbled through the solution at -25°C for 5 min. The cooling bath was

- removed and the mixture allowed to warm to 20°C of The solvents were solution was stirred for 16 h under Ar. The solvents were removed by rotary evaporation, and the residue was diluted with dichloromethane and extracted with dilute aqueous HCl. The organic layer was concentrated to afford unreacted Cbz
 - valinal (4.02 g). The acidic aqueous layer was basified with 1N NaOH and extracted with dichloromethane, the organic extract was concentrated and the residue purified by flash chromatography (4% methanol in dichloromethane) to provide the title compound as a white solid (50 mg) NMR (CD₃OD) δ
 - 30 7.29 (5H, m), 5.04 (2H, dd), 4.38 (1H, dd), 2.06 (6H, s), 2.01 (1H, m), 0.93 (3H, d), 0.77 (3H, d).

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- The benzyloxycarbonyl@group.wasscleaved_bygandg
- hydrogenolysis using the same procedure as described previously in Example 1(b) except using the product of 1(a) (50 mg), to afford the title compound as a white solid

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- -NdO par (24 mg, 87%) NMR (CDCl'3) 8 4.11 (2H, s(br)), 3.71 (1H, d), 2.06 (6H, s), 2.00 (1H, m), 0.71 (6H, dd). ASSA A MENT DOMESTICE
 - c) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-tbutyldimethylsiloxy-N-[1'-isopropyl-1'-(4,5-dimethyl) imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide

Using the procedure of Example 1(c), except substituting (2R, 4S, 5S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-6-phenyl-2-phenylmethylhexanoic acid and (1S)-1-(4,5-

dimethylimidazol-2-yl)-2-methylpropylamine (24 mg), the title compound was prepared (55 mg, 57%). NMR (CDCI3) & 7.26-6.80 (10H, m), 4.65 (1H, d), 4.24 (1H, dd), 3.87 (1H, q), 3.61

(1H, m), 2.77-2.39 (5H, m), 2.22 (1H, m), 1.98 (6H, s), 1.79

- 00.8 (1H, m), 1.58 (1H, m), 1.24 (9H, s), 0.85 (9H, s), 0.69 (6H, 15.(d); 0.06 (6H, d).
- d) (2R, 4s, 5s, 1's) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'isopropyl-1 - (4,5-dimethyl) imidazol-2-yl]methyl-6-phenyl-2phenylmethyl-hexanamide (h. wedge-)
- By following the deprotection procedure described in Example 1(d), except using (2R, 4S, 5S, 1'S) -5-(tbutoxycarbonyl)amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-10.5 1 - (4,5-dimethyl) imidazol-2-yl]methyl-6-phenyl-2phenylmethyl-hexanamide (55 mg) and omitting the final 25 treatment with methanolic HCl, the title compound was
- (1H, (br d), 4.47 (1H, m), 4.29 (1H, m), 3.58 (2H, m), 2.84-2.51 (5H, m), 2.20 (1H, m), 2.04 (6H, s), 1.71 (2H, m), 1.38

(9H, s), 0.69 (6H, dd). THE BOOK FOR THE STATE OF THE S

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Example 10 CACCOUNTING THE CAR ADMINISTRATION AND LOSS ASSESSMENT

Preparation of (2R-4s, 5s, 1's) -5-(t-butoxycarbonyl) amino-4hydroxy-N-[1'-isopropyl-1'-(4.5-dimethyl)imidazol-2-35 <u>yllmethyl-6-phenyl-2-phenylmethyl-hexanamide</u>

> a) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(4phenylimidazol-2-yl)methane

Using the procedure of Example 1 (a) except using Cbz-(L)-valine (2.19 g) and α-ketophenylacetaldehyde instead of glyoxal, the title compound was prepared (1.54 g, 48%).

NMR(CDCl₃) δ 7.62 (1H, (br)), 7.24 (10H, m), 5.79 (1H, d),

5.04 (2H, dd), 4.32 (1H, dd), 2.31 (1H, m), 0.96 (3H, d)

- 5 5.04 (2H, dd), 4.32 (1H, dd), 2.31 (1H, m), 0.96 (3H, d), 0.79 (3H, d); MS m/e 350.4 [M+H], 199.0.
- b) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-phenyl) imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide

Using the procedure of Example 1(b)-1(c), except using the compound of 10(a) (72 mg), the title compound was prepared (67 mg, 44%). NMR(CDCl₃) & 7.70 (1H, d), 7.40-6.71 (16H, m), 4.73 (1H, d), 4.54 (1H, dd), 3.96 (1H, q), 3.69 (1H, m), 2.88-2.36 (5H, m), 1.73 (2H, m), 1.33 (9H, s), 0.91 (9H, s), 0.84 (6H, dd), 0.11 (6H, d); MS m/e 725.4 [M+H]+.

c) (2R, 4S, 5S, 1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N[1'-isopropyl-1'-(4-phenyl)imidazol-2-yl]methyl-6-phenyl-2phenylmethyl-hexanamide

Using the procedure of Example 9(d), except starting from (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-phenyl)imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide (67 mg), the title compound was prepared (30 mg, 54%). NMR(CDCl₃) & 7.52-6.67 (16H, m), 5.48 (1H, d), 3.60 (1H, q), 3.44 (1H, d), 2.60 (4H, m), 1.96 (1H, m), 1.62 (2H, m), 1.23 (9H, s), 0.73 (3H, d), 0.62 (3H, d); MS m/e 611.4 [M+H]+, 242.2, 195.0, 150.2.

Example 11

Preparation of (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(N'-methyl)imidazol-2-yllmethyl-6phenyl-2-phenylmethyl-hexanamide

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a) (1S)-carb benzyl xyamino-1-isopropyl-1-(N'-methylimidazol-
2-yl)methane
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The product of Example 1(a) (273 mg, 1 mmol) was heated at 40°C for 2 h in methyl iodide (5 mL). The reaction 5 mixture was evaporated, and the residue was suspended in aqueous Na₂CO₃. The mixture was extracted with

dichloromethane, dried (Na₂CO₃) and concentrated. The crude product was purified by flash chromatography (silica, 2% methanol/dichloromethane) to yield the title compound (200

10 mg, 70%). NMR (CDCl₃) δ 7.29 (5H, s), 6.92 (1H, s), 6.69 (1H, s), 5.94 (1H, d), 5.03 (2H, q), 4.55 (1H, dd), 3.64 (3H, s),

Call Marie Carres (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-(2)

of the King the many bearant by the second do

, (po 15 butyldimethylsiloxy-N-[1'-isopropyl-1'-(N'-methyl)imidazol-2rott (1991) yl]methyl-6-phenyl-2-phenylmethyl-hexanamide (1991)

fig w be be to Tollowing the procedure of Example (1 (b) -1 (c) a except using the compound of 11(a) (90 mg), the title compound was prepared (104 mg, 50%). NMR (CDCl₃) δ 7.32-6.89 (10H, m),

bao1320 6.81 (1H, s), 6.59 (1H, s), 6.08 (1H, d), 4.71 (2H, m), 3.94 (1H, [q], [q], [3.70], (1H, [m], 3.25], (3H, [s], 2.80-2.36], (5H, [m], 2.21ета (р(1H, m) р. 1.73 (2H, m) , 1.31 (9H, s), 0.94 (9H, s), 0.85 (6H, dd), 0.11 (6H, s).a by again ye

-- 25:32c) (2R, 4S, 5S, 1'S) -5 (t-butoxycarbonyl) amino-4-hydroxy-N-[1'isopropyl-1:-:(N'-methyl) imidazol-2-yl]methyl-6-phenyl-2-The vphenylmethyl-hexanamide 4837 in postal of the safe

monal (888 % % Following the procedure of Example 9(d), except using (3000) 01(2R,4S 5S,1'S)-5-(t-butoxycr-bonyl)amino-4-t-034 and

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, (30) Mebutyldimethylsiloxy-N-[1:'-isopropyl-1'-(N'-methyl)imidazol-2yl]methyl-6-phenyl-2-phenylmethyl-hexanamide (100 mg), the title compound was prepared (74 mg, 89%). NMR(CDCl₃) δ 7.21-6.74 (11H, m), 6.70 (1H, s), 6.59 (1H, s), 4.95 (1H, d), 4.61 - Tynnicam ((1H, dd), 3.60. (3H, m), 3.48 (3H, s), 2.71 (5H, m), 2.06 (1H, m), 1.64 $(2H_{AB}m)$, 1.32 $(9H_{AB}s)$, 0.82 (3H, d), 0.63 (3H, d); * ********* MS, m/e 549.3 [M+H] + 1 for a mathematic section in the fi

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Example 12 rejocios and Discon

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-

5 (3-phenylpropargyl)hexanamide of the first first of so is

a) (3R,5S,1'S) - (1'-t-butoxycarbonylamino-2'-phenyl) ethyl-3-(3-phenylpropargyl) -tetrahydrofuran-2-one (3-phenylpropargyl)

To a solution of lithium diisopropylamide (3:61 mL, 2.0 M in THF, 2.2 eq) in THF at -78°C under an argon atmosphere, (5S,1'S)-(1'-t-butoxycarbonylamino-2'-phenyl)ethyl-tetrahydrofuran-2-one (1.0 g, 1.0 eq) was added. After stirring at -78°C for 15 min, hexamethylphosphoramide (1.14 mL, 2 eq) was added, and stirring was continued an additional 10 min. Phenylpropargyl bromide (1.28 g, 2.0 eq),

- was added and the resulting mixture was stirred at -78°C for 2 h, then poured into dilute aqueous HCl and extracted with dichloromethane. The combined organic extracts were evaporated under reduced pressure to an oil, which was
- 20 chromatographed (silica, 20% ethyl acetate/hexanes) to afford the title compound as a white solid (0.455 g, (33%)) (11) (CDCl3) & 7.18 (10H, m), 4.50 ((2H, m)), 3.93 (1H, q), 2.79 (5H, m), 2.23 (2H, m), 1.24 (9H, s).
 - 25 b) (2R, 4S, 5S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethyl-siloxy-6-phenyl-2-(3-phenylpropargyl) hexanoic acid:

The title compound (496 mg, 84%) was prepared by the procedure of Evans et al., J. Org. Chem. 50, 4615 (1985) from the product of 12(a) (450 mg)...... NMR (CDCl₃) δ 7.49-7.10 (10H,

- - c) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-tbutyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl6-phenyl-2-(3-phenylpropargyl) hexanamide

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Following the procedure of Example 1(c), except using (2R, 4S, 5S)-5-(t-butoxycarbonyl)amino-4-t-butyldimethylsiloxy-6-phenyl-2-(3-phenylpropargyl)hexanoic acid (240 mg) and

(1S)-1-imidazol-2-yl-2-m thylpropylamine, the title compound was prepared (244 mg, 84%). NMR(CDCl₃) & 7.14 (12H, m), 6.72 (1H, d), 4.58 (1H, d), 4.49 (1H, dd), 3.92 (1H, q), 3.80 (1H, m), 2.54 (5H, m), 1.65 (2H, m), 1.20 (9H, s), 0.81 (9H, s), 0.80 (6H, dd), 0.05 (6H, d).

- (2R, 4S, 5S, 1'S) = 5 (t-butoxycarbonyl) amino-4-hydroxy-N-(1'- isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-(3- isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-yl) methyl
 - 10 the see Following the procedure of Example 9(d), except using (2R, 4S, 5S, 1'S) = 5-(t-butoxycarbonyl) amino-4-t-
- butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl6-phenyl-2-(3-phenylpropargyl)hexanamide, the title compound
 was prepared (161 mg, 79%). NMR(CDCl₃) & 7.24-6.98 (10H, m),
 155 6.68 (2H, 8), 5.20 (1H, m), 4.52 (1H, d), 3.49 (2H, m), 3.06
 16.0 (1H, m), 2.56 (5H, m), 2.04 (1H, m), 1.61 (2H, m), 1.26 (9H,
 s), 0.68 (6H, dd); MS m/e 581.2 (M+Na)+, 559.2 [M+H]+, 541.4,
 503.2, 485.2, 459.2, 441.2.

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Preparation of (2R.4S.5S.1'S)-5-(isopropoxycarbonyl) amino-4
Shydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2
Colored phenylmethyl-hexanamide and the state of the state of

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- 25 nearing is the second feature for the second feature of the second se
- The product of Example 1(c) (0.20 g, 0.31 mmol) was the following trifluoroacetic acid and stirred at room of the fittemperature for 5 min, and partitioned between the construction of the dichloromethane and saturated aqueous Na₂CO₃. The organic extract was dried over Na₂CO₃, filtered and evaporated to (0.17 g, 100%) which was used 35 (without further purification.)
 - b) (2R, 4S, 5S, 1'S) -5-(isopropoxycarbonyl) amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-(N'-

isopropoxycarbonyl) imidazol-2-yl] methyl-6-phenyl-2-

A mixture containing the compound of 13(a) (0.17 g, 0.31 mmol), isopropyl chloroformate (0.62 mL, 1M in the containing the compound of 13(a) (0.17 g, 0.31

- dichloromethane, 2 eq) and 4-dimethylaminopyridine (0.75 g, 2 eq) in dichloromethane (40 mL) was allowed to stir at room temperature overnight under an argon atmosphere. The mixture was then partitioned between dichloromethanemand saturated aqueous Na₂CO₃, and the organic extract was dried over Na₂CO₃.
- The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica, 4% 6 9 methanol/dichloromethane) to afford the title compound (0.214 g, 96%). NMR (CDCl₃) δ₁7.35-6.78 (12H, m), 6.57 (1H, d), 5.61 (1H, dd), 5.19 (1H, m), 4.86 (1H, m), 4.77 (1H, d), 3.97 (1H, q), 3.63 (1H, t), 2.88 (1H, dd), 2.70-2.48 (4H, m), 2.06 (1H, m), 2.00-1.85 (1H, m), 1.79-1.64 (1H, m), 1.45 (6H, dd), 0.94 (9H, s), 0.85 (6H, d), 0.12 (6H, d)
 - c) (2R, 4S, 5S, 1'S) -5-(isopropoxycarbonyl) amino-4-hydroxy-N(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2phenylmethyl-hexanamide

methanol, excess aqueous HCli(~65 eq) was added. The resulting solution was allowed to stir at room temperature

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overnight, and was concentrated under reduced pressure. The residue was diluted with H2O, and basified with aqueous Na₂CO₃. The mixture was extracted with dichloromethane, and the combined organic extracts were dried over Na₂CO₃. The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica, 4% methanol/dichloromethane) to afford the title compound (0.150 g, 97%) NMR(CDCl₃) & 7.32-6.96 (13H, m), 5.48 (1H, d), 5.08 (1H, m), 5.00 (1H, s(br)), 4.87 (1H, m), 3.78 (1H, m), 3.62 (1H, m), 3.25 (1H, m), 2.96-

2.67 (4H, m), 2.29 (1H, m), 1.95-1.65 (2H, m), 1.25-1.12 (6H,

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35 dd), 0.80-0.60 (6H, dd); MS m/e 521 [M+H]+, 519 (M-H)-.

- (** 10) 17.0 . Example 14. . . (**)

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Preparation of (2R.4S.5S.1'S)-5-(benzyloxyethoxycarbonyl)

amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6phenyl-2-phenylmethyl-hexanamiden with 150 methyl-6-

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To a solution of 2-benzyloxyethanol (2.5 g, 16.4 mmol)

and bis (4-nitrophenyl) carbonate (5.0 g, 1 eq) in

dichloromethane (200 mL), N-methylmorpholine (1.81 mL, 1 eq)

was added. The resulting mixture was allowed to stir at room

temperature for 3 d. The reaction mixture was washed successively with H20 and saturated aqueous NaCl and dried over Na2SO4. The solvent was removed in vacuo, and the

residue was purified by flash chromatography (silica, 20%

ethyl acetate/hexanes) to afford the title compound (4.38 g, 30 84%). NMR(CDCl3) & 8.26 (2H, m), 7.34 (7H, m), 4.62 (2H, s), 4.49 (2H, t), 3.70 (2H, t).

b) (2R, 4S, 5S, 1'S) -5- (benzyloxyethoxycarbonyl) amino-4-t-fyriconing butyldimethylsiloxy-N-[1'-isopropyl-1'-(N'-benzyloxyethoxy35 carbonyl) imidazol-2-yl] methyl-6-phenyl-2-phenylmethyl-1.

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mg, 0.24 mmol) in dichloromethane (40 mL) under an argon

atmosphere, benzyloxyethyl 4-nitrophenyl carbonate (160 mg, 2 eq) and 4-dimethylaminopyridine (60 mg/c2req) were added. The resulting mixture was allowed to stirkate room temperature with dichloromethane. The organic extract was washed successively with aqueous Na₂CO₃, H₂O, aqueous Na₂CO₃ and H₂O, and dried over Na₂CO₃ w The solvent by the was removed in vacuo, and the residue was purified by flash chromatography (silica, 4% methanol/dichloromethane) to afford the title compound (180 mg, 82%) \sim NMR (CDCl₃) δ 7.45-型 4 10 46.80%(22H, m), 6.62次(1H, d), 5.60次(1H, t), 35.06%(1H, d), 4.60 - 37、出 、(c - (2H, s), 4.52 (2H, s), 4.50) (2H, m); 4.31g (1H, m); 4.07 (2H, (m + m), (m), (m)2.77-2.41 (4H, m), 2.09 (1H, m), 1.90 (1H, m), 1.73 (1H, m), 0.95 (9H, s), 0.81 (6H, dd), 0.11 (6H, d).

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(2R, 4S, 5S, 1'S) -5- (benzyloxyethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide viada

Following the procedure of Example 13(c), except using the compound of Example 14(b) #(160 mg) # the title compound was prepared (100 mg, $\{818\}$). NMR(CDCl₃, CD₃OD) δ 7.40-6.79 (17H, m), 4.55 (2H, s), 4.45 (1H, d), 4.20 (2H, m), 3.80-3.45 ($9.6 \times 1.0 \times (5H, m)$, 2.95-2.66 (4H, m), 2.59 (1H, dd), 9.2.07 (1H, m), 1.71 HOCK // 2 (2H, Tm) & 0.80 (3H, Ad) , -0.68 (3H, Ad) . AT /

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Preparation of (2R.4S.5S.1'S)-5-(methoxycarbonvl) amino-4hydroxy-N-(1'-isopropyl-1'-imidazol-2-vl)methyl-6-phenyl-2-

() 30 phenylmethyl-hexanamide of vol. 9 % (althou) years (grass

a) (2R, 4S, 5S, 1'S) - 5 - (methoxycarbonyl) amino-4-tbutyldimethylsiloxy-N-[1'-isopropyl-1'-(N'-1, 186) 40 methoxycarbonyl)imidazol-2-yl]methyl-6-phenyl-2-phenylmethylhexanamide Company of the company of

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Following the procedure of Example 13(b), except using (2R, 4S, 5S, 1'S) -5-amino-4-t-butyldimethylsiloxy-N-(1'isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-

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2.1 (m2.15 (#C) 3) 2.5% 2.03

- hexanamide, the title compound was prepared (89%).

 NMR(CDCl₃) δ 7.40-6.79 (12H, m), 6.52 (1H, d), 5.58 (1H, dd),

 4.91 (1H, d), 3.96 (3H, s), 3.95 (1H, d), 3.66 (1H, t), 3.60

 (3H, s), 2.85 (1H, m), 2.73-2.40 (4H, m), 2.08 (1H, m), 1.90

 5 (1H, m), 1.69 (1H, m), 0.95 (9H, s), 0.85 (6H, dd), 0.14 (6H, d).
 - b) (2R, 4S, 5S, 1'S) -5-(methoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide
- Following the procedure of Example 13(c), except using the compound of Example 15(a), the title compound was prepared (70%)... NMR(CDCl₃, CD₃OD) δ 7.23-6.60 (12H, m), 4.38 (1H, d), 3.65 (1H, t), 3.54 (3H, s), 3.33 (1H, m), 2.95 (1H, 15 m), 2.82-2.40 (4H, m), 1.95 (1H, m), 1.64 (2H, m), 0.69 (6H, dd).

Part - Charles - Example 16

- Preparation of (2R.4S.5S.1'S)-5-(ethoxycarbonyl)amino-4
 (a) hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2
 (a) (b) phenylmethyl-hexanamide
 - a) (2R, 4S, 5S, 1'S) -5-(ethoxycarbonyl) amino-4-t-

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- ethoxycarbonyl)imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-
- paress describe Following the procedure of Example 13(b), except using as (2R,4S,5S,1'S)-5-amino-4-t-butyldimethylsiloxy-N-(1'-
- 00.3034 isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
- (HI) (N. Shexanamide and ethylchloroformate, the title compound was
- d), 5.60 (1H, dd), 4.86 (1H, d), 4.41 (2H, m), 4.15-3.90 (3H,
 - m), 3.66 (1H, t), 2.87 (1H, \dot{m}), 2.75-2.45 (4H, \dot{m}), 2.08 (1H,
 - 35 m), 1.92 (1H, m), 1.70 (1H, m), 1.45 (3H, t), 1.18 (3H, t), 0.98 (9H, s), 0.85 (6H, dd), 0.13 (6H, d).

b) (2R, 4S, 5S, 1'S) -5- (ethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 13(c), except using the compound of Example 16(a), the title compound was prepared (95%). NMR(CDCl₃, CD₃OD) δ 7.25-6.75 (12H, m), 4.43 (1H, d), 3.95 (2H, q), 3.61 (1H, q), 3.40 (1H, m), 2.85 (1H, m), 2.80-2.40 (4H, m), 2.05 (1H, m), 1.61 (2H, t), 1.11 (3H, t), 0.72 (3H, d), 0.55 (3H, t).

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Example: 17 gains, to?

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a) (3R,5S,1'S)-(1'-t-butoxycarbonylamino-2'-phenyl)ethyl-3-(3-phenylprop-2-enyl)-tetrahydrofuran-2-one

Following the procedure of Example 12(a), except using cinnamyl bromide (0.485 mL) as the alkylating agent, the title compound was prepared (0.51.g, 75%). NMR (CDCl₃) δ 7.35-7.10 (10H, m), 6.43 (1H, d), 6.09 (1H, m), 4.60 (1H, m), 4.48 (1H, q), 4.00 (1H, t (br)), 2.96-2.55 (4H, m), 2.53-2.21 (2H, m), 2.05 (1H, m), 1.35 (9H, s).

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b) (2R,4S,5S)-5-(t-butoxycarbonyl)amino-4-t-butyldimethyl-siloxy-6-phenyl-2-(3-phenyl-2-propenyl)hexanoic acid

Following the procedure of Example 12 (b), except using the compound of Example 17 (a), the title compound was prepared (77%). NMR(CDCl₃) δ 7.40-7.05 (10H, m), 6.48-6.00 (4H, m), 4.78 (1H, d), 3.94 (1H, q), 3.80 (1H, m), 2.89 (1H, m), 2.83-2.26 (4H, m), 1.90 (1H, m), 1.59 (1H, m), 1.28 (9H, s), 0.90 (9H, s), 0.08 (6H, d).

```
(i) (iii) (c) (2R,4S,5S,1'S)=5-(t-butoxycarbonyl) amino-4-t-()
          butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-
          6-phenyl-2-(3-phenyl-2-propenyl) hexanamide
which is figure Following the procedure of Example 1(c), except using
  5 % the compound of 17 (b), the title compound was prepared (82%).
       MMR (CDCl<sub>3</sub>): \delta 7.35-7.15 (10H, m), \sigma7.14-6.85 (2H, m), 6.73 (1H,
   .0 114 (1H, d), 6.10-5388 (1H, m), 4.78 (1H, d), 4.65 (1H,
  % example t), 3.97 (1H, q), w3.76 (1H, m), (2.77 (2H, d), 2.50-2.25 (2H,
   Har of m ), 2.12 (1H, m), 61.70 (1H, m), 1.63 (1H, m), 1.36 (9H, s),
      10 % 0.92 (9H, %s), 0.81 (6H, %d), 0.09 (6H, %d). 3 mg fms was
       CARL I st ( (will restrance lividge discommendation of a second of
          d) (2R, 4S, 5S, 1'S) - 5 - (t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
      isopropyl-1:-imidazol-2-yl)methyl-6-phenyl-2-(3-phenyl-2-
(All) (T. propenyl) hexanamide (C.) (All controls of
                                                    Half (15,HE) (E.Following) the procedure of Example 9(d), except using
      the compound of 17(c), the title compound was prepared (90%).
          NMR (CDCl<sub>3</sub>, CD<sub>3</sub>OD) \delta37.30=7.00 (10H, m), 6.71 (2H, s), 6.26
          (1H, d), 6.41 (1H, m), 3.66 (1H, d), 3.50 (1H, d), 2.88-2.45
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20 m), 1.34 (9H, s), 0.88 (3H, d), 0.74 (3H, d) coby (21) 88.0 .em MS m/e/561 4[M+H]+! To brough a diff to or dain a baleon of the most of the bale of the The said of the state and a necessial selection and a selection of the compound that the compound

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4-5 .BEhvdroxy-N-[1'-isopropyl-1'-(4-nitroimidazol-2-vl)]methvl-6phenyl-2-phenylmethyl-hexanamide . Coff 2007.

tan your ner i 36 mg, deal and used without fur hear

(4H, m); 2.36 (1H, m); 2.23 (1H, m); 2.06 (1H, m); 1.70 (2H,

a) (1S)-N-(1-:(imidazol-2-yl)-2-methyl)propylacetamide -530 Gardain Total solution of the compound of Example 1(b) (175 mg) in dichloromethane (10 mL) at 00°C was added disopropylentire ethylamine) (355 mg, 82.75 mmol) followed by acetyl chloride -yachbary (215 mg/c2:75 mmol) . Theoresulting mixture was stirred overnight,) washed with saturated aqueous Na₂CO₃, and 50.35% oconcentrated. The residue was treated with methanol, stirred (L) (overnight and concentrated under reduced pressure to afford The title compound (181 mg, 78%) as a white solid. δ (2H, s), MMR (CD₃OD) δ 6.95 (2H, s), 4.72 (1H, d, J=6 Hz), 2.35-2.10

(1H, m), 1.98 (3H, s), 0.98 (3H, d, - たがつって (3円, Hz), 12 (3H, d, c) (3H, d, d) (3H, d) (3

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- b) (1S)-N-(1-(4-nitroimidazol-2-yl)-2-methyl) propylacetamide

 The compound of Example 18(a) (290 mg; 1.60 mmol) was
 dissolved in cold concentrated H2SO4 (2 mL), and after
 stirring for 15 min, 90% HNO3 (0.4 mL) was added dropwise.

 The resulting mixture was slowly warmed to 40°C and stirred
 for 2 h. The mixture was then poured onto ice; and the pH
 was adjusted to 4 by the addition of solid NaHCO3. The
 mixture was extracted with ethyl acetate (6x), and the
 combined organic extracts were dried over MgSO4 and
 concentrated under reduced pressure to afford the title
 compound (153 mg, 42%). NMR(CD3OD) 8 7.98 (1H, s), 4.70 (1H,
- 15 d, J=6 Hz), 2.35-2.15 (1H, m), 1.98 (3H, s), 0.95 (3H, d, J=5 (2)) (3H, d, J=5 Hz); MS m/e 475.2 (2M+Na)+, 249.2 (M+Na)+, 227.2 [M+H]+, 185.2 168.0 (0.0000), 10000
 - (1S)-1-(4-nitroimidazol-2-yl)-2-methylpropylamine,

(11) 61. (1) 6.7 (1) 6.6 (1) 1. (1) 1

20 dihydrochloride salt (6 180) 00.0 (6 10) 4811 (6 1

A mixture of the compound of Example 18(b) (153 mg, 0.68 mmol) in 6N HCl (2 mL) was heated at 90°C for 12 h, cooled and concentrated under reduced pressure. The title compound was obtained (138 mg, 80%) and used without further

- 25 purification., NMR (CD3OD) 8.12 (1H, s), 04:30 (1H, d, J=4 Hz), 2.45-2.30 (1H, m), 1.12 (3H, 1d, J=4 Hz), 0:90 (3H, d, J=4 Hz).
 - (i.) (2R, 4S, 5S, 1'S) -5- (t-butoxycarbonyl) amino-4-t- (i.)
- 30 butyldimethylsiloxy-N-[1!-isopropyl-1!-(4-nitroimidazol-2-(y)] methyl-6-phenyl-2-phenylmethyl-hexanamide(6) (4)

Following the procedure of Example 1(c), except using (2R, 4S, 5S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-6-phenyl-2-phenylmethylhexanoic acids and (1S)-1-(4-a)

nitroimidazol-2-yl)-2-methylpropylamine, the title compound was prepared. NMR(CDCl₃) δ 7.30-6.90 (10 H, m), 6.60 (1H, d, J=4 Hz), 4.70 (1H, d, J=5 Hz), 4.40 (1H, t, J=4 Hz), 3.90 (1H, q, J=4 Hz), 3.75 (1H, dd, J=8, 3 Hz), 2.75-2.30 (6H, m),

1.80-1.50 (2H, m), 1.25 (9H, s), 0.85 (9H, s), 0.70 (6H, m), 0.05 (6H, d, J=4 Hz).

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e) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-5-isopropyl-1'-(4-nitroimidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the deprotection procedure of Example 1(d),
except using (the compound of Example 18(d), the title
compound was prepared. NMR(CD₃OD) δ 7.90 (1H, s), 7.40-6.90
(10H, m), 4.53 (1H, d, J=6 Hz), 3.70 (1H, m), 3.50 (1H, m),
2.90-2.60 (5H, m), 2.00 (1H, m), 1.90-1.55 (2H, m), 1.49 (9H,
s), 0.85 (3H, d, J=4 Hz), 0.70 (d, 3H, J=4 Hz); MS m/e 602.4
(M+Na)+, 580.4 [M+H]+, 524.4, 480.4.

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Example 19

Preparation of (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-(1'-ethyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide

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a) (1S)-1-carbobenzyloxyamino-1-ethyl-1-(imidazol-2-yl)methane

Following the procedure of Example 1(a), except using Cbz-(L)-α-ethylglycinal in place of valinal, the title

25 (20 compound was prepared. NMR(CDCl3) δ 7.45-7.10 (5H, m), 6.90

(2H, ms), 5.65 (1H, d, J=6.Hz), 5.10-4.95 (2H, m), 4.40 (1H, q, J=5 Hz), 2.00-1.70 (2H, m), 1.00-0.80 (3H, m).

が (15) - (1-imidazol-2-yl) propylamine () で () je

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30 Following the procedure of Example 1(b), except using the compound of Example 19(a), the title compound was prepared. NMR (CDCl₃) δ 6.90 (2H, s), 5.00-4.50 (2H, br s), 4.00 (1H, t, J=5 Hz), 2.00-1.70 (2H, m), 1.00-0.80 (3H, m).

butyldimethylsiloxy-N-[1'-ethyl-1'-imidazol-2-vl]methyl-6phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 1 (c), except using 5 (2R, 4S, 5S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-6-phenyl-2-phenylmethylhexanoic acid and the compound of Example 19(c), the title compound was prepared. NMR (CDCl₃) δ 7.35-6.90 (10H, \cdot m), 6.78 (2H, \cdot s), 6.20 \cdot (d, \cdot J=5.4Hz), 4.80-4.65 (2H, m), 4.05 (1H, g, J=5 Hz), 3.72" (1H, dd, J=10), 3 Hz), 2.90-2.50 (5H, m), 2.10-2.05 (1H, m), 1.90-1.65 (3H, m), 1.40 (9H, s), 0.95 (9H, s), 0.90-0.85 (3H, m), 0.50 (6H, s).

> d) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'ethyl-1'-imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-

hexanamide 15

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Following the procedure of Example 9(d), except using the compound of Example 19(c), the title compound was prepared. NMR(CD3OD) δ 7.40-7.00 (10H, m), 6.85 (2H, s), 3.60-3.50 (2H, m), 2.95-2.60 (5H, m), 1.95-1.52 (4H, m), 1.48-1.26 (9H, m), 0.8-0.9 (3H, m). MS m/e 521.2 [M+H]+; 503.4, 447.4. (10.4860-1.4681)

(1) 1.20 P. (1) 基础

Example 20 below for

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25 Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hvdroxy-N-(1'-propyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide (825 0) record to the same of

Following the procedure of Example 19(a)-19(d), except 30 substituting Cbz-(L)-α-propylglycinal for Cbz-(L)-α- ως ethylglycinal, the title compound was prepared Data for the intermediates of this synthesis were: 986 1986 1986

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b) (1S)-1-(imidazol-2-yl)butylamine. NMR(CDCl₃) δ 6.90 (2H, s), 5.10-4.40 (2H, s(br)), 4.05 (1H, t, J=5 Hz), 1.90-1.55 (2H, m), 1.45-1.20 (4H, m), 0.95-0.80 (3H, m).

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- 8.c) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-N-[1'-propyl-1'-imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide. NMR(CDCl₃) δ 7.35-7.00 (10H, m), 6.78 (2H, s), 6.22 (1H, d, J=5 Hz), 4.85-4.68 (2H, m), 4.00 (1H, q, J=3 Hz), 3.75 (1H, dd, J=10, 3 Hz), 2.80-2.50 (5H, m), 2.12-1.95 (1H, m), 1.90-1.60 (3H, m), 1.40-1.20 (13H, m), 0.90 (9H, s), 0.87-0.80 (3H, m), 0.07 (6H, s).
 - d) (2R, 4S, 5S, 1'S)-5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'20 propyl-1'-imidazol-2-yl]methyl-6-phenyl-2-phenylmethylhexanamide. NMR(CD₃OD) δ 7.40-7.00 (10H, m), 6.90 (2H, s),
 3.78-3.50 (2H, m), 2.90-2.60 (5H, m), 1.90-1.55 (4H, m),
 1.45-1.20 (13H, m); MS m/e 535.4 [M+H]+

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contracted for the store of the after and, early the testing

hydroxy-N-[1'-isopropyl-1'-(4-bromoimidazol-2-yl)]methyl-6phenyl-2-phenylmethyl-hexanamide

First (87) but have a contaderant make of the transfer

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- (BP) Data (1S)-N-1-(4-bromoimidazol-2-yl)-2-methylpropylacetamide
 - (1S)-N-1-(4,5-dibromoimidazol-2-yl)-2-methylpropylacetamide
 - 35 Smethylpropylacetamide (1.58 g, 8.73 mmol) in 95% ethanol (30 mL), 2,4,4,6-tetrabromocyclohexadienone (3.93 g, 9.60 mmol) was added. The resulting mixture was stirred at room temperature for 30 min, and was concentrated in vacuo. The

residue was dissolved in dichloromethane, washed with aqueous NaHCO3 and dried over Na2SO4. The solvent was removed in vacuo, and the residue was purified by flash chromatography to afford the title compound (650 mg, 29%) NMR(CDCl3) δ
5 7.70 (1H, d, J=7 Hz), 6.85 (1H, s), 4.67 (1H, t; J=7 Hz), 2.35-2.25 (1H, m), 1.95 (3H, s), 1.05 (3H, d, J=5 Hz), 0.80 (3H, d, J=5 Hz).

Also isolated was (1S)-N-1-(4,5-dibromoimidazol-2-yl)-2-methylpropylacetamide (50 mg, 8%): NMR(CDCl₃), δ 4.68 (1H, t, J=7 Hz), 2.38-2.25 (1H, m), 2.05 (3H, s), 1.05 (3H, d, J=5 Hz), 0.85 (3H, d, J=5 Hz); MS m/e 340.0 [M+H]+, 280.8.

b) (1s)-1-(4-bromoimidazol-2-yl)-2-methylpropylamine,
dihydrochloride (8 48) 6 (m 201)

introduced by the control of the property of the property of the property of the control of the property of the control of the

Following the procedure of Example 18(c), except using (1S)-N-1-(4-bromoimidazol-2-yl)-2-methylpropylacetamide, the title compound was prepared. NMR(CD₃OD) δ 7.60 (1H, s), 4.35 (1H, d, J=7 Hz), 2.50-2.38 (1H, m), 1.10 (3H, d, J=5 Hz), 0.82 (3H, d, J=5 Hz).

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c) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t- butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-bromoimidazol-2-yl)] methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 1(c), except using

(2R, 4S, 5S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy6-phenyl-2-phenylmethylhexanoic acid and (1S)-1-(4bromoimidazol-2-yl)-2-methylpropylamine dihydrochloride, the
title compound was prepared. NMR(CDCl₃) δ 7.40-7.00 (10H,
m), 6.70 (1H, s), 6.45 (1H, d, J=5 Hz), 4.80 (1H, d, J=6 Hz),

30 4.40 (1H, t, J=5 Hz), 4.02 (1H, q, J=4 Hz), 3.78 (1H, dd,
J=7, 2 Hz), 2.90-2.30 (9H, m), 1.85-1.60 (2H, m), 1.45 (9H,

d) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'isopropyl-1'-(4-bromoimidazol-2-yl)] methyl-6-phenyl-2-ag
phenylmethyl-hexanamide or register (2000)

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Following the procedure of Example 9(d) except using (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-t-butyldimethyl-

s), 1.00 (9H, s), 0.85 (6H, t, J=4 Hz), 0.10 (6H, d, J=6 Hz).

siloxy-N-[1!-isopropyl-1'-(4-bromoimidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide, the title compound was prepared. NMR(CDCl₃) & 7.40-7.00 (10H, m), 6.70 (1H, s), 6.55 (1H, m), 4.90 (1H, d, J=5 Hz), 4.50 (1H, t, J=5 Hz), 3.75-3.55 (2H, m), 2.95-2.65 (5H, m), 2.40-2.25 (1H, m), 1.90-1.60 (2H, m), 1.48 (9H, s), 0.80 (6H, t, J=6 Hz).

MS m/e 613.2 [M+H]+; 535.2.

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速 2000 (Example 22) 2000 (2) (No. 2) (Example 22) 2000 (2) (Examp

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Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4.5-dibromoimidazol-2-yl)]methyl6-phenyl-2-phenylmethyl-hexanamide

(if 15 course Following the procedures of Examples 18(c)-18(d) and (1849(d), mexcept substituting (1S)-N-1-(4,5-dibromoimidazol-2-00000 of y))-2-methylpropylacetamide for (1S)-N-(1-4-nitroimidazol-2-00000 fyl)-2methyl) propylacetamide, the title compound was prepared.

(if 15 course Fyl)-2methyl) propylacetamide, the title compound was prepared.

(if 20 course Fyl)-2methyl) propylacetamide, the title compound was prepared.

- a) (1S)-1=(4,5-dibromoimidazol-2-yl)-2-methylpropylamine,

 3 28 5 dihydrochloride: NMR(CD3OD), 8,4.10-3.90 (1H, br.s), 2.30
 -24.7 8 (2.100(1H, s(br)), 1.10 (3H, d, J=5 Hz), 0.85 (3H, d, J=5 Hz).
- b) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-butyl-dimethylsiloxy-N-[1'-isopropyl-1'-(4,5-dibromoimidazol-2-yl)] methyl-6-phenyl-2-phenylmethyl-hexanamide. NMR(CDCl₃) 8 7.40-6.90 (10H, m), 6.38 (1H, d, J=5 Hz), 4.80-4.50 (3H, m), 4.00 (1H, q, J=5 Hz), 3.72 (1H, dd, J=7, 2 Hz), 2.85-2.50 (5H, m), 2.30 (1H, br s), 2.20-2.05 (1H, m), 1.85-1.65 (2H, m), 1.38 (9H, s), 0.90 (9H, s), 0.80-0.60 (6H, m), 0.10 (6H, dd, J=3 Hz).
- bloc c) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-35 sisopropyl-1'-(4,5-dibromoimidazol-2-yl)] methyl-6-phenyl-2-phenylmethyl-hexanamide. NMR(CDCl₃) δ:7.35-6.85 (10H, m), 6.65 (1H, br s), 4.92 (1H,1d, J=4 Hz), 4.50 (1H, m), 3.72-(H2) 3.50 (2H, m), 2.98-2.63 (5H, m), 2.15-2.02 (1H, m), 1.90-1.70

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(2H, m), 1.40 (9H, s); MS m/e (693.03[M+H]+; 637, 619, 593,and the 575,7291. The land of the control length and of the country The state of the control of the giocoly with the exercising

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** [1.30] (1.40) (1.40) (1.40) (1.40) (1.40) (1.40) (1.40) (1.40) (1.40) (1.40)

a Profession (1986) (1997) call Example 23 (報名) 過度におせて、色 (18

Preparation of (2R.4S.5S.1'S)-5-(t-butoxvcarbonvl)amino-4hvdroxy-N-[1'-isopropyl-1'-(4-methylimidazol-2-yl)]methyl-6phenyl-2-phenylmethyl-hexanamide

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methylimidazol-2-yl)methane. World White Programmed

Cbz-(L)-valinal (1.0 g, 3.9 mmol) and pyruvaldehyde (4.3 mmol, 40% in H₂O) were dissolved in methanol (10 mL) and 15 chilled in an ice bath. Concentrated aqueous ammonia (2 mL) was added and the reaction mixture was stirred at 20°C overnight. The solvent was removed in vacuo and the residue barrage of dissolved in 5% HCl (50, mL) and extracted with ethyl acetate relies (3x20 mL). The aqueous layer was basified to pHalo with solid Na₂CO₃. A tan solid (463 mg) precipitated. The solid was purified by flash chromatography (silica, 2%-3% methanol/dichloromethane) to yield the title compound as a white solid (180 mg, 16%). The solid (180 mg, 16%) white solid (180 mg, 16%) mp 163-164°C; NMR (CDCl3) δ 7.45-7.35 (5H, m), 6.60 (1H, s), 6.00 (1H, d, J=4 Hz), 5.05 (2H, 25 q, J=4 Hz), 4.40 (1H, t, J=4 Hz), 2.45-2.30 (1H, m), 2.20 (3H, s), 0.95 (3H, d, J=4 Hz), 0.80 (3H, d, J=4 Hz); MS m/e 2 (16 0 575.4 (2M+H)+, 288.0 [M+H]+ 10 2 - 1 yunade 0 - 1 yulland (17

b) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino 4-t 4 t 30 butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-methylimidazol-2yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide

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Following the procedure of Example 1(b)-1(c), except using (2R, 4S, 5S) -5-(t-butoxycarbonyl) amino-4-tbutyldimethylsiloxy-6-phenyl-2-phenylmethylhexanoic acid and 35 the compound of Example 23(a), the title compound was prepared. NMR (CDCl₃) δ 7.37-6.90 (10H, m), 6.45 (1H, s), 6.38 (1H, d, J=3 Hz), 4.75 (1H, d, J=5 Hz), 4.40 (1H, t, J=5 Hz), 3.95 (1H, q, J=4 Hz), 3.72-3.68 (1H, m), 2.90-2.70 (4H,

m), 2.60=2.48 (1H, m), 2.45-2.30 (1H, m), 2.17 (3H, s), 1.90-1.80 (1H, m), 1.75-1.62 (1H, m), 1.40 (9H, s), 0.95 (9H, s), 0.75 (6H, t, J=3 Hz), 0.10 (6H, d, J=2 Hz).

isopropyl-1'-(4-methylimidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 9(d), except using the compound of Example 23(b), the title compound was 10 prepared. NMR(CDCl₃) δ 7.38-7.00 (10H, m), 6.52 (1H, s), 4.92 (1H, d, J=5 Hz), 4.42 (1H, t, J=4 Hz), 3.72-3.55 (2H, m), 2.95-2.65 (5H, m), 2.35-2.20 (1H, m), 2.18 (3H, s), 1.75 (2H, br s), 1.42 (9H, s), 0.75 (6H, d, J=3 Hz); MS m/e 549.2 [M+H]⁺.

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, (iii) S as $(L_{\infty}(E)) = 0.0$, (i.e. fit **Example 24**).

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4-trifluoromethylimidazol-220 yl) lmethyl-6-phenyl-2-phenylmethyl-hexanamide

a) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(4-

Sodium acetate trihydrate (5.35 g, 2.2 eq) was dissolved (25 in water (16 mL) and 1,1 dibromotrifluoroacetone (5.31 g, 1.1 eq) was added. The solution was stirred for 30 min at 90°C. The solution was cooled to 0°C and poured into a 0°C solution of Cbz-Valinal (4.22 g, 1.0 eq) in anhydrous methanol (80 mL). Concentrated ammonium hydroxide (22 mL) was added and 30 the mixture stirred overnight at room temperature. The solvents were evaporated to give a white precipitate which was covered with 150 mL of water. The suspension was filtered and the solid washed twice with water. The white solid was dissolved in ethyl acetate, dried over sodium sulfate,

35 filtered, and evaporated to a white solid (5.24 g, 86%).

1HNMR(CD3OD) & 7.45 (1H, s), 7.40-7.20 (5H, m), 5.05 (2H, q, J=4 Hz), 4.50 (1H, d, J=4 Hz), 2.38-2.10 (1H, m), 1.00 (3H, d, J=4 Hz), 0.80 (3H, d, J=4 Hz), 13CNMR(CD3OD, 1H-decoupled)

δ 18.9, 19.4, 67, 117 (q, J=3 Hz), 123.2 (q, $\tilde{J}=266$ Hz), 128.7, 129.3, 133 (q, J=39 Hz), 138.0, 151.7; MS $\tilde{m}/e^{\frac{13}{3}}$ 342.0 [M+H]+.

b) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-butyl-dimethylsiloxy-N-[1'-isopropyl-1'-(4-trifluoromethylimidazol-2-yl)] methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 1(b)-1(c), except using the compound of Example 24(a) and (2R,4S,5S)-5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-6-phenyl-2-phenylmethylhexanoic acid, the title compound was prepared.

NMR(CDCl₃) δ 7.35-6.95 (11 H, m), 6.50 (1H, d, J=4 Hz), 4.75 (1H, d, J=6 Hz), 4.25 (1H, t, J=4 Hz), 3.95 (1H, q, J=4 Hz), 3.80-3.68 (1H, m), 2.90-2.40 (5H, m), 1.80-1.60 (2H, m), 1.35 (9H, s), 0.90 (9H, s), 0.80 (3H, d, J=3 Hz), 0.70 (3H, d, J=3 Hz), 0.05 (6H, d, J=2 Hz).

c) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'-isopropyl-1'-(4-trifluoromethylimidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 9(d), except using the compound of Example 24(b), the title compound was prepared. NMR(CDCl₃) 8 7.35 (1H, s), 7.25-6.90 (10H, m), 4.53 (1H, d, J=5 Hz), 3.68 (1H, t, J=4 Hz), 3.52 (1H, d, J=6 Hz), 2.90-2.55 (5H, m), 2.10-1.95 (1H, m), 1.85-1.70 (1H, m), 1.65-1.50 (1H, m), 1.40-1.25 (9H, m), 0.90 (3H, d, J=4 Hz), 0.65 (3H, d, J=4 Hz); MS m/e 603.2 [M+H]+, 529.2, 503.2.

Example 25) Lenk SV sel do

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- Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-methyl-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6phenyl-2-phenylmethyl-hexanamide
 - a) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(imidazol-2-yl)methane

Following the procedure of Example 1(a), except substituting N-methyl-Cbz-(L)-valinal for Cbz-(L)-valinal, the title compound was prepared. NMR(CDCl3) 8 7.45-7.30 (5H.

m), 6.90 (2H, s), 5.12 (2H, s), 4.60 (1H, d, J=6 Hz), 2.95 (3H, s), 2.70-2.53 (1H, m), 1.02 (3H, d, J=3 Hz), 0.85 (3H, d, J=3 Hz).

b) (1S)-1-methylamino-1-isopropyl-1-(imidazol-2-yl) methane Following the procedure of Example 1(b), except using the compound of Example 25(a), the title compound was prepared. NMR(CDCl₃) δ 6.95 (2H, s), 3.52 (1H, d, J=3 Hz), 2.30 (3H, s), 2.10-1.90 (1H, m), 0.98 (3H, d, J=3 Hz), 0.82 (3H, d, J=3 Hz).

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- Following the procedure of Example 1(c), except using the compound of Example 25(b), the title compound was prepared. NMR(CDCl₃) δ 7.40-6.72 (12H, m), 4.82 (1H, d, J=5 Hz), 3.95 (1H, q, J=4 Hz), 3.82-3.75 (1H, m), 2.95-2.70 (5H, m), 2.51 (2H, s), 2.50-2.38 (1H, m), 2.08 (1H, s), 1.87-1.68 (2H, m), 1.38 (9H, s), 0.95 (9H, s), 0.88 (3H, d, J=3 Hz), 0.75 (3H, d, J=3 Hz), 0.05 (6H, d, J=7 Hz).

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Following the procedure of Example 9(d), except using the compound of Example 28(c), the title compound was prepared. NMR(CDCl₃) δ 7.35-6.82 (12H, m), 4.90-4.72 (1H, m), 3.70-3.00 (2H, m), 2.92-2.50 (8H, m), 1.90-1.60 (2H, m), 30 1.40-1.30 (9H, m), 0.95-0.70 (6H, m).

MS m/e 549.2 [M+H]⁺.

en a casa agreem of the wave of **Example 26** to provide an

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'-isopropyl-1'-(4-carbomethoxyimidazol-2-yl)lmethyl-6-phenyl-2-phenylmethyl-hexanamide

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a) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(4- (1) trimethoxymethylimidazol-2-yl)methane(10) (2)

Sodium methoxide (8 mL, 25% in methanol, 37.5 mmol) was added to a solution of the compound of Example 27(a) (640 mg, 1.88 mmol) in anhydrous methanol (10 mL). The resulting mixture was heated at 55°C overnight, cooled, and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and H₂O, and the organic extract was dried over Na₂CO₃. The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica, 2% methanol/dichloromethane) to afford the title compound (545 mg, 77%). NMR(CDCl₃) & 7.40-7.20 (5H, m), 6.98 (1H, br s), 5.90 (1H, br s), 5.08 (2H, s), 4.50 (1H, br s), 3.15 (9H, s), 2.00 (1H, m (br)), 1.00-0.80 (6H, m); MS m/e 378.2 [M+H]+, 346, 332, 271, 195.

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A solution of the compound of Example 26(a) (540 mg) in 1:1 methanol/aqueous HCl (10 mL) was stirred at room temperature for 2 h, and concentrated under reduced pressure. The residue was partitioned between aqueous Na₂CO₃ and dichloromethane, and the organic extract was dried over Na₂CO₃ and concentrated in vacuo to afford the title compound (470 mg, 75%). NMR(CDCl₃) δ 7.55 (1H, br(s), 7.35 (5H, s), 5.90-5.65 (1H, m), 5.10 (2H, t, J=4 Hz), 4.60-4.42 (1H, m), 3.88 (3H, s), 2.40 (1H, br s), 1.00-0.80 (6H, m); MS m/e 332.2 [M+H]⁺.

30 c) (1S)-1-amino-1-isopropyl-1-(4-carbomethoxyimidazol-2-a yl)methane

Following the procedure of Example 1(b), except using the compound of Example 26(b), the title compound was prepared. NMR(CDCl₃) δ 7.62 (1H, s), 3.97 (1H, d, J=4 Hz),

35 3.82 (3H, s), 2.27-2.05 (1H, m), 0.95-0.75 (6H, m).

4 (P.)

The 15.0 Following the procedure of Example 9(d), except using the compound of Example 26(d), the title compound was prepared. NMR(CDCl3) & 7.40-6.80 (12H, m), 4.90 (1H, d, J=5 2.68 (5H, m), 2.45-2.30 (1H, m), 1.80-1.60 (2H, m), 1.40 (9H, M), 2.00 (2H, M), 1.40 (9H, M), 1.60 (2H, M), 1.40 (9H, M

Example 27 to the last war with

25 f) Preparation of (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-isopropyl-1'-(4-methylcarbonylimidazol-2-yl) lmethyl-6-phenyl-2-phenylmethyl-hexanamide

- 30 % hydroxymethylimidazol-2-yl)methane.

 30 % hydroxymethylimidazol-2-y
- solution (sat.) and stirred for 1 h. The solution was extracted with dichloromethane twice and the combined organic

extracts were washed successively with saturated aqueous Rochelles salt and brine. The organic layer was dried over magnesium sulfate, filtered, and evaporated to give the title ्राय के design of the solid of (0.27; g/(94%) विश्व NMR (CDCI₃) δ 7.25 5 (5H, s), 6.69 (1H, s), 6.14 (1H, d), 5.01 (2H, dd), 4.52 (2H, s), 4.37(1H, t), 2.19 (1H, m), 0.92 (3H, d), 0.73 (3H, d); MS 3m/e 304.0 [M+H]+... ↑ A (1) 3 = (b (RI) ST. A (18

F. V. (at (3H) 03 - V.F. (8 (M) 69.5) (m)

🔧 - b) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(4- 🐎 🕹

formylimidazol-2-yl)methane. However, by (80), Of Org (82)

The compound of Example 27(a) (0.11 g, 1.0 eq) was stirred in anhydrous dichloromethane at room temperature under an inert argon atmosphere. Manganese dioxide (0.126 g, 4.0 eq) was added and the mixture was stirred at room 15 temperature overnight. After 16;h and additional 2.0 eg of manganese dioxide was added. The reaction was complete by TLC after 2 h. The mixture was filtered through a pad of Celite® and the filter cake was washed with dichloromethane. The organic solvent was removed in vacuo to give the title $(0.075 \pm g)$, (69%) NMR(CDCl₃) (69%) NMR(CDCl₃) (69%)(1H,s), 7.54 (1H, s), 7.12 (5H, s), 6.435 (1H, d), 4.96 (2H, dd), 4.43 (1H, t), 2.08 (1H, m), 0.91 (3H, d), 0.62 (3H, t);

25 c) (1S, 1'RS) -1-carbobenzyloxyamino-1-isopropyl-1-(4-(1'-

MS m/e $302.0 [M+H]^+$.

The compound of Example 27(b) 20(0.10g/1.00eq) was stirred in a 3:1 ether/THF mixture at 0°C under an argon atmosphere. Methyl magnesium bromide (0.47 ml, 3.0M in THF, 4.0 eq) was added and allowed to stire at 0°C for 1:5 h.45 The solution was diluted with 5% aqueous HCl and made basic with solid sodium carbonate. The solution was extracted with ethyl acetate three times and the combined organic extracts were dried over sodium carbonate, filtered, and evaporated to δ 35 a white solid (0.1 g, 95%). NMR(CDCl₃); δ 7.19 (5H,s), 6.59 (1H, s), 6.42 (1H, d), 4.92 (2H, dd), 4.73 (1H, m), 2.09 (1H, om), 1.37 (3H, d), 0.82 (3H, d), 0.66 (3H, d). to attained.

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The compound of Example 27(c) (0.1 g, 1.0 eq) was stirred in anhydrous methanol with 10% Pd on activated carbon (0.020 g). Hydrogen gas was bubbled through the solution via balloon for 1 h and the reaction was maintained under a hydrogen atmosphere for 3 h. The mixture was filtered through a pad of Celite® and the filter cake washed with methanol. The methanol was evaporated to give the title compound as a white solid (0.05 g, 87%). NMR(CDCl3) & 6.63 (1H, s), 4.72 (1H, dd), 3.61 (1H, d), 1.92 (1H, m), 1.49 (3H, dd), 0.84 (3H, d), 0.67 (3H, d).

(2R, 4S, 5S, 1 S, 1 RS) -5-(t-butoxycarbonyl) amino-4-t-15 butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-(1''-hydroxyethyl)imidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide To a solution of (2R,4S,5S)-5-(t-butoxycarbonyl)amino-4-- Control to the control of the cont in the green (0, 131 g) (1.0 eq) win anhydrous dimethylformamide, with 20 compound of Example 27(d) (50 mg, 1.1 eq), BOP reagent Can (0:11 g, 1.0 eq), and triethylamine (0.04 mL, 1.0 eq) were HEADE Maddedigs The solution was stirred at room temperature for a. 78% at 16% how The solution was diluted with water and extracted three times with dichloromethane. The combined organic extracts were washed with water, then brine. The solution was dried over magnesium sulfate, filtered, and evaporated to give a ballo rewhite foam that foam was chromatographed (silica, 4% of the intemethanol/dichloromethane) to afford the title compound as a white foam (0.11 g, 65%). NMR (CDCl₃) δ 7.31-6.54 (12H, m), 6 30 4.72 (1H, d), 4.48 (2H, d), 3.82 (1H, q), 3.61 (1H, m), 2.81-00.F (42.3)(6H, m),01.65((3H, m), 1.48((3H, d), 1.22((9H)))s), 0.89 0%.0% (9H, 9%s), 10.70%(3H, d), 3%0.61.(3H, d), 10.06%(6H, s); MS m/e 693.4 [M+H] + 1044) Since also be a to it so to it of a term

f) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-tbutyldimethylsiloxy-N-[1'-isopropyl-1'-(4-methylcarbonylimidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide

The compound of Example 27(e) (45 mg, 1.0 eq) was stirred in dry dichloromethane under an inert argon atmosphere. Manganese dioxide (23 mg, 4.0 eq) was added and the mixture was stirred at room temperature for 16 h. An additional 2.0 eq of manganese dioxide was added and the reaction was complete by TLC after 2.5 h. The mixture was filtered through a pad of Celite® and the filter cake was washed with dichloromethane. The organic solvent was evaporated to give the title compound as a white solid (0.038 g, 85%). NMR(CDCl₃) & 7.49-6.76 (11H, m), 6.30 (1H, br d), 4.71 (2H, m), 3.86 (1H, q), 3.61 (1H, dd), 2.77-2.41 (5H, m), 2.31 (3H, s), 1.58 (2H, m), 1.20 (9H, s), 0.83 (9H, s), 0.69 (6H, dd), 0.04 (6H, d); MS m/e 691.4 [M+H]+.

g) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-isopropyl-1'-(4-methylcarbonylimidazol-2-yl)] methyl-6-phenyl-20 2-phenylmethyl-hexanamide

out at (Polatives) to no delive a or

The compound of Example 27(f) (38 mg, 1.0 eq) was stirred in anhydrous THF under an argon atmosphere at room temperature. Tetrabutyl ammonium fluoride (0.33 mL, 1.0M in THF, 6.0 eq) was added and the solution stirred for 16 h.

25 The solution was diluted with water and extracted three times with dichloromethane. The combined organic extracts were washed with water and evaporated to a white solid. The solid was covered with diethyl ether, decanted twice, and dried to give the title compound as a white solid) (25 mg, 79%).

30 NMR(CDCl₃) & 7.14 (5H, m), 6.86 (5H, m), 5.14 (1H, d), 4.42 (1H, d), 3.58 (1H, q), 3.45 (1H, d), 2.80-2.50 (5H, m), 1.91 (1H, m), 1.63 (2H, m), 1.26 (9H, s) (rotamer observed), 0.70 (3H, d), 0.57 (3H, d); MS m/e 577.2 [M+H]⁺.

(b (38) 80.6 (b (t) ve.g (b) Example 28

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'-isopropyl-1'-(4-isopropylcarbonylimidazol-2-yl)lmethyl-6-phenyl-2-phenylmethyl-hexanamide

pairs 3 a) (1S, 1'RS)-1-carbobenzyloxyamino-1-isopropyl-1-(4-(1'pairs hydroxy-2'-methyl) propylimidazol-2-yl) methane.

only observe Following the procedure of Example 27(c), except using

(\$10 isopropyl magnesium bromide (1.024 mL, 2.0M solution, 4.0 eq)

in place of methyl magnesium bromide, to yield a crude

product. The crude product was chromatographed (silica, 4%

methanol/dichloromethane) to yield the title compound as a

white solid (0.155 g , 88%). NMR(CDCl3) & 7.19 (5H, m), 6.58

15 (1H, s), 4.91 (2H, m), 4.38 (1H, q), 4.20 (1H, dd), 2.11 (1H,

m), 1.83 (1H, m), 0.72 (12H, m); MS m/e 346.2 [M+H]+; 328.2,

279.0 (254.0, 205.0, 177.0, 149.0, 118.0.

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c) (2R,4S,5S,1'S,1''RS)-5-(t-butoxycarbonyl)amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-(1''-hydroxy-2''-methyl)propylimidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-m30 % hexanamide as a second contact of the seco

Following the procedure of Example 27(e), except using the compound of Example 31(b) (96 mg, 1.1 eq), substituting dimethyl formamide as the solvent instead of dichloromethane, and purifying the product by chromatography, the title compound was prepared (168 g, 57%). NMR(CDCl₃) δ 7.22-6.81 (11H, m), 6.62 (1H, d), 4.71 (1H, dd), 4.53 (1H, t), 4.19 (1H, d), 3.82 (1H, q), 3.58 (1H, dd), 2.71-2.30 (5H, m), 2.03 (24(1H, m), 1.70 (1H, m), 1.57 (1H, m), 1.14 (9H, s), 0.91 (3H,

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d), 0.88 (9H, s), 0.78 (3H, d), 0.67 (3H, d), 0.59 (3H, d), 0.03 6H, d); MS m/e 721.4 [M+H]⁺.

- d) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-isopropylcarbonylimidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide

 Following the procedure of Example 27(f), except using
 the compound of 31(c) (168 mg, 1.0 eq) and chromatographing
 the crude product (silica, 3% methanol/dichloromethane) the
 title compound was prepared as a white solid (132 mg, 79%).

 NMR(CDCl₃) & 7.20-6.76 (11H, m), 5.05 (1H, br, m), 3.88 (1H,
 q), 3.61, m), 3.19 (1H, m), 2.80-2.46 (5H, m), 2.22 (1H, m),
 2.07 (1H, m), 1.63 (1H, m), 1.15 (16H, m), 0.89 (9H, s),
 0.74 (6H, m), 0.08 (6H, d), MS m/e 719.4 [M+H]+
 - e) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-isopropyl-1'-(4-isopropylcarbonylimidazol-2-yl)] methyl-6-phenyl-2-phenylmethyl-hexanamide
- Following the procedure of Example 27(g), except using the compound of Example 31(d) (132 mg), the title compound was prepared as a white foam (90 mg, 81%). NMR(CDCl₃) δ 7.48 (1H, s), 7.11 (5H, m), 6.82 (5H, m), 5.29 (1H; d), 4.46 (1H, m), 3.54 (1H, q), 3.48 (1H, m), 3.14 (1H, m), 2.74-2.44 (5H, m), 1.90 (1H, m), 1.61 (2H, m), 1.28 (9H, s) ((rotamers observed), 1.13 (6H, m), 0.69 (3H, d), 0.48 (3H, d); MS m/e 605.2 [M+H]⁺.

Example 29 Lylydowilde

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(a) (a) (a) (b) (b) (b) (b) (b) (b) (b) (c) (c) (c) (c) (c)

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- Preparation of (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4-phenylcarbonyl-imidazol-2yl)lmethyl-6-phenyl-2-phenylmethyl-hexanamide
 - a) (1S,1'RS)-1-carbobenzyloxyamino-1-isopropyl-1-(4-(1'-hydroxy)benzylimidazol-2-yl)methane
- Following the procedure of Example 27(c) we except substituting phenylmagnesium bromide (0.45 mL, 3.0M solution, 4.0 eq) for methyl magnesium bromide, and chromatographing

the crude product (silica, 3% methanol/dichloromethan) th

- (viii) (q. title compound was prepared as a white solid (175 mg, 96%).

NMR (CDCl₃) δ 7.26 (1H, d), 7.11 (10H, m), 6.39 (1H, dd), 6.08

(1H₇, d), 5.63 (1H, d), 4.82 (2H, m), 4.29 (1H, m), 2.01 (1H, 5 m), 0.76 (3H, m), 0.59 (3H, d).

(m (ME)b) ((1S,1!RS)-1-amino-1-isopropyl-1-(4-(1'-hydroxy)benzyl-(m (MS)-imidazol-2-yl)methane(m (ME) (ME) (ME) (ME) (ME) (ME)

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- the compound of Example 29(a) (98 mg) the title compound was prepared as a tacky white foam (65 mg, 98%).

hydroxy)benzylimidazol-2-yl)]methyl-6-phenyl-2-phenylmethylhexanamide

Following the procedure of Example 27(e), except using

the compound of Example 29(b) (0.065 g, 1.1 eq), and chromatographing the crude product (2% methanol/ dichloromethane) the title compound was prepared as a white solid (109 mg, 55%). NMR(CDCl₃) & 7.48-6.79 (16H, m), 4.77 (1H, m), 33.88 (1H, m), 3.61 (1H, m), 2.65 (4H, m), 2.39 (1H, M), 2.15 (1H, m), 1.94 (1H, m), 1.75 (1H, m), 1.56 (1H, m), 1.21 (9H, s) (rotamers observed), 0.86 (9H, s), 0.68 (6H,

5 dd), 0.07 (6H, s); MS m/e 755.4 [M+H]+.

d) ((2R,4S,5S,1'S)-5-(t-butoxycarbonyl) amino-4-t-butyl-dimethylsiloxy-N-[1'-isopropyl-1'-(4-phenylcarbonylimidazol-2-yl)] methyl-6-phenyl-2-phenylmethyl-hexanamide

pa30 grapp to Following the procedure Example 27(f), except using the end (compound of Example 29(c) (109 mg, 1.0, eq), the title

compound was prepared as a white solid (80 mg, 74%).

NMR (CDCl3) & 7.49-6.84 (17H, m), 3.88 (1H, q), 3.63 (1H, t),

(a) 08 2.87-2.49 (6H, m), 2.11 (2H, m), 1.64 (1H, m), 1.11 (9H, s),

(a) 35 (0.82 (9H, s), 0.71 (6H, dd), 0.06 (6H, d); MS m/e 753.4

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e) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-isopropyl-1'-(4-phenylcarbonylimidazol-2-yl)] methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 27(g), except using the compound of Example 29(d) (80 mg, 1.0 eq), the title compound was prepared as a white solid (45 mg, 74%).

NMR(CDCl₃) δ 7.84-6.77 (16H, m), 4.48-(1H, d), 3.59 (1H, m), 3.42 (1H, m), 2.80-2.54 (5H, m), 1.99 (1H, m), 1.63 (2H, m), 1.26 (9H, s) (rotamers observed), 0.73 (3H, d), 0.59 (3H, d); 10 MS m/e 639.2 [M+H]+.

Example 30

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Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4-formylimidazol-2-yl)]methyl-6phenyl-2-phenylmethyl-hexanamide

a) (1S,1'RS)-1-amino-1-isopropyl-1-(4-(hydroxy)methyl-imidazol-2-yl)methane. Of the analysis of the amount of the

gradit of the following the condition of the second of the following the

Following the procedure of Example 27(d), except using the compound of Example 27(a) (90 mg), the titled compound was prepared (50 mg, 100%). NMR(CDCl₃) δ 6.85((1H, s), 4.62 (2H, s), 3.85 (1H, d, J=4 Hz), 2.20-2.05 (1H, m), 0.88 (6H, d, J=5 Hz).

b) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-(hydroxy) methyl-imidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide

40 , 0.00 (60) s), WE EVE - SELE IN 18 511.

Following the procedure of Example 27(e) mexcept using the compound of Example 30(a) (50 mg), and chromatographing the crude product (silica, 2% methanol/dichloromethane) the title compound was prepared (130 mg, 65%). NMR (CDCl₃) δ 7.30-6.95 (11H, m), 4.82 (1H, d), 4.50-4.60 (1H, m), 4.40 (1H, d), 3.90-4.00 (1H, m), 3.60-3.68 (1H, m), 2.45-2.80 (5H, m), 2.20-2.30 (1H, m), 1.75-1.85 (1H, m), 1.60-1.70 (1H, m), 1.30 (9H, s), 0.95 (9H, s), 0.75 (3H, d), 0.62 (3H, d), 0.05 (6H, d).

- c) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-tbutyldimethylsiloxy-N-[1'-isopropyl-1'-(4-formylimidazol-2yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide
- Following the procedure of Example 27(f), except using the compound of Example 30(b) (50 mg), the title compound was prepared (20 mg, 40%). NMR(CDCl₃) δ 9.80(0.5H, s), 9.64

 (0.5H, s), 7.50-6.90 (11H, m), 6.52-6.42 (1H, m), 4.88-4.70 (2H, m), 4.42-4.32 (1H, m), 4.02-3.93 (1H, m), 3.78-3.71 (1H, m), 2.90-2.40 (5H, m), 2.30-2.19 (1H, m), 1.87-1.62 (2H, m), 1.45 (9H, s), 0.95 (9H, s), 0.87-0.72 (6H, m), 0.05 (6H, m)
 - d) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'| (a | | isopropyl-1'-(4-formylimidazol-2-yl)] methyl-6-phenyl-2-

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15 phenylmethyl-hexanamide of neolar transfer that the

(rotamers).

Following the procedure of Example 27(g), except using the compound of Example 30(c) (20 mg), the title compound was prepared (12 mg, 71%). NMR(CD3OD) & 9.60 (1H, s), 7.65 (1H, s), 7.20-6.90 (10H, m), 4.52 (1H, d), 3.60 (1H, m), 3.45 (1H, 20 d), 2.80-2.45 (5H, m), 2.00-1.88 (1H, m), 1.75-1.65 (1H, m), (01.62-1.45)(1H, m), 1.27 (9H, s), 0.82 (3H, d), 0.62 (3H, d); MS m/e 563.4, 242.2, 204.8.

Example 31

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Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4-(hydroxymethyl)-imidazol-2yl)lmethyl-6-phenyl-2-phenylmethyl-hexanamide

The compound of Example 30 (b) (40 mg), the title compound was prepared (20 mg). NMR(CD3OD) δ 7.27-6.92 (10H, s), 6.72 (1H, c), 3.64-3.60 (1H, m), 3.48 (1H, d), 2.82-2.50 (5H, m), 2.03-1.92 (1H, m), 1.78-1.67 (1H, m), 1.63-1.49 (1H, 35.0 m), 1.28 (9H, s), 0.80 (3H, d), 0.65 (3H, d); MS m/e 565.4.

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Preparation of (2R,4S,5S,1'S)-5-((tetrahydrothiopyran-4-yl)oxycarbonyl)amino-4-hydroxy-N-(1''-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide (10) 013 6

propried (20 mg, 10%). Noticentally a series of

Following the procedures of Example 14 (a)-14 (c),
except using 4-hydroxytetrahydrothiopyran in place of 2benzyloxyethanol, the title compound was prepared.

10 Analytical data for the intermediates of this synthesis were:

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1.5 230

- b) (2R, 4S, 5S, 1'S) -5-((tetrahydrothiopyran-4-yl) oxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6phenyl-2-phenylmethyl-hexanamide. NMR(CD3OD) 87.12-6.65
 - (10H, m), 6.64 (2H, s), 5.60 (1H, d), 4.36 (2H, m), 3.58 (1H, c), q), 3.49 (1H, d), 2.68-2.48 (6H, m), 2.44+2.30 (3H, m), 1.93-1.74 (3H, m), 1.70-1.40 (4H, m), 0.61 (3H, Ed), 0.50 (3H, d).

Example 33

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Preparation of (2R.4S.5S.1'S)-5-((tetrahydro-4H-pyran-4-yl)oxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide

(55) 69, 2009-1-98 (15 % P.) 76 (65)

- pollowing the procedures of Example 14(a)-14(c), except using 4-hydroxytetrahydro-4H-pyran in place of 2- and benzyloxyethanol, the title compound was prepared.

 Analytical data for the intermediates of this synthesis were:
 - a) (tetrahydro-4H-pyran-4-yl)-(4-nitro)phenylcarbonate.
 NMR(CDCl₃) δ 8.32 (1H, s), 8.28 (1H, s), 7.41 (1H, s), 7.38 (1H, s), 5.00 (1H, m), 4.05-2.90 (2H, m), 3.68-3.49 (2H, m), 2.17-2.00 (2H, m), 1.95-1.75 (2H, m).

```
b) (2R, 4S, 5S, 1'S) -5- ((tetrahydro-4H-pyran-4-yl) oxycarbonyl) -
                                              amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
phenyl-2-phenylmethyl-hexanamide. NMR (CD<sub>3</sub>OD) δ 7.16-6.89
    ist ex5age (10H, m), 6.79 (2H, s), 4.54 (2H, m), 3.82-3.70 (2H, m),
                                      -3.69-3.62 (1H, m), 3.50-3.46 (1H, m), 3.45-3.35 (2H, m),
    (3H, m), 2.00 (1H, m), 1.82-1.62
                                              (3H, m), (1.55-1.45 (2H, m), 1.37 (1H, m), 0.79 (3H, d), 0.63
         AND FIGURE OF THE CONTRACTOR OF THE STATE OF
                        10 h all all merzem had to mail termine
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July the last (general synchronic speciel Example 34) and the

Preparation of (2R.4S.5S.1'S)-5-(4-picolinyloxy)amino-4-List to hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide

esos colide a la baza seo ef. la selp eviplica e la la trans-(3) (4.1) To be The compound of Example 1(d) was dissolved in neat TFA. $\mathcal{A}(x)$. Fr After: 10 (min : the solution was) concentrated to provide the amine salt, \((2R,4S,5S,1'S)-5-amino-4-hydroxy-N-(1'-isopropyl-

a differ by designing property and to be able to be a first

1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide olympo trifluoroacetate. (IThis amine salt (25 mg, 1.eq) was | files | dissolved in DMF, and (4-picolinium-(p-nitro) phenyl-carbonate pairs sep-nitrophenylate (23 mg, 1) eq) and triethylamine (0.04 mL, 5) busingenceq) (were added. on The mixture was stirred funder Ar for 17 h. 0' ... 25 (% Water was added and the mixture was extracted with

(Fi) 90 dichloromethane. (The organic extracts were concentrated and the residue was triturated with ether to yield the title . NMR (CD3OD) δ 8.52 (2H, d), 7.10 (14H, m), 6.87 (2H, s), 5.07 (2H, dd), 4.61 (1H, d), 3.80 (1H, m), 30-13.59_(1H, m);, 2.77-c(5H, m); 2.05 (1H, m), 1.83 (1H, m), 1.60 - - Lvd(1H, m), -0.842,(3H, -d), 0.59 (3H, d) a - ray 1 - 27 Held

The two about the (t.b) be a (profit () Example 35, the profit of the second

April 35: 1 sangrag err beres est a dia navign wery of the area (4 (3)) Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl) amino-4-87.5 Am hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(PR) and (4.4.4-trifluorobut-1-yl)hexanamide

radi provo ignoro (tali signist) so atti como o selletto i

a) (3R,5S,1'S)-(1'-t-butoxycarbonylamino-2'-phenyl)ethyl-3-(4,4,4-trifluorobut-1-yl)-tetrahydrofuran-2-onedis

To a solution of lithium diisopropyl amide (1.8 mL of a 5 1.5M solution, 2.2 eq) in tetrahydrofuran (10 mL) was added (5S, 1'S)-(1'-t-butoxycarbonylamino-2'-phenyl)ethyltetrahydrofuran-2-one (0.50 g; 1.0 eq) in anhydrous THF (2 mL) at -78°C. After stirring for 15 min at -78°C, hexamethylphosphoramide (0.57 mL, 2.0 eq) was added to the solution. The solution was stirred for several min and 1,1,1-trifluoro-4-iodobutane (0.78 g, 2.0 eq) was added. After 2 h at -78°C, the reaction mixture was quenched with a 10% aqueous HCl and extracted with dichloromethane. organic extracts were combined and evaporated to a clear oil. The oil was chromatographed (silica, 2%) methanol/ dichloromethane) to give the title compound as a white foam (0.248 g, 37%). NMR: (CDC13) δ 7.18 δ (5Ha, m), 4.57 (1H; d), 4.41 (1H , dd), 3.95 (1H , q); 2.82 (2H, d); 2:55 (2H , m),

2.49-1.49 (7H , m), 1.32 (9H , s); MS m/e 438.0 (M+Na)+.

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b) (2R, 4S, 5S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethyl-- siloxy-6-phenyl-2-(4,4,4-trifluorobut-1-yl)hexanoic acid

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Following the procedure of Example 12(b), except using the compound of Example 35(a) (245 mg); the title compound was prepared (215 mg, 67%). NMR (CDCl3) δ 7.18 (5H/m m), 4.70 (1H, d), 3.88 (1H, q), 3.69 (2H, m), 2.73 (1H, m), 2.38 (1H, m), 1.91 (2H, m), 1.45 (6H, m), 1.31 (9H, s) (rotamers observed), 0.90 (9H, s), 0.08 (6H, d); MS m/e548.2 [M+H]+.

c) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6phenyl-2-(4,4,4-trifluorobut-1-yl)hexanamide 2 30 20

Following the procedure of Example 1(c), except using the compound of Example 35(b) (100 mg) and (1S)-1-imidazol-2-yl-2-methylpropylamine, the title compound was prepared (83 mg, 68%). NMR (CDCl₃) δ 7.22 (5H, m), 7.03 (1H, d), 6.89 (2H, s), 4.72 (1H, d), 4.51 (1H, t), 3.91 (1H, q), 3.65 (1H, m), 2.78 (2H, d), 2.33 (2H, m), 1.82 (4H, m), 1.48 (4H, m), 1.36 (9H,

two singlets; rotamers present), 0.99 (9H, s), 0.91 (3H, d), 0.79 (3H, d), 0.07 (6H, d); MS m/e669.4 [M+H]+.

5 isopropyl-1:-imidazol-2-yl)methyl-6-phenyl-2-(4,4,4-trifluorobut-1-yl)hexanamide

Following the procedure of Example 9(d), except using the compound of Example 35(c) (83 mg), the title compound was prepared (40 mg, 58%). NMR(CD3OD) & 7.19 (5H, m), 6.92 (2H, 10 s), 4.61 (1H, d), 3.64 (1H, q), 3.48 (1H, m), 2.79 (2H, m), 2.49 (1H, m), 2.13 (4H, m), 1.60 (5H, m), 1.36 (9H, s), 0.90 (3H, d), 0.71 (3H, d); MS m/e555.2 [M+H]+.

the tolde dillifedit - . . Example 36

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Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(t-&8.4-) butoxycarbonyl)amino-6-phenyl-N-(1'-isobutyl-1'-(imidazo-2-(ML) & & yl))methyl-hexanamide hydrochloride

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20 10 a) 2-(1'-carbobenzyloxyamino-1'-isobutyl) methyl-imidazole

[Hold 1.07] Following the procedure of Example 1(a), except
substituting Cbz-isoleucinal (1.83 g) for Cbz-valinal, the
title compound was prepared (0.658 g, 31%). NMR(CDCl3) δ

6.96 (2H, s), 5.31 (1H, d), 4.48 (1H, dd), 2.15 (1H, m), 1.44

25 (9H, s), 1.17 (2H, m), 0.92 (3H, t), 0.82 (3H, d); MS

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- b) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl) amino-6-phenyl-N-(1'-isobutyl-1'-(imidazo-2-yl)) methyl-hexanamide hydrochloride
- substituting the procedure of Example 1(b)-1(d), except substituting the compound of Example 36(a) for (1's)-1'- carbobenzyloxyamino-1'-isopropyl-1'-(imidazo-2-yl)methane, the title compound was prepared. NMR(DMSO-d6) & 7.90 (1H,d),
 - 35 7.29-7.02 (10H, m), 6.89 (2H,s), 6.50 (1H,d), 4.81 (1H,m), 4.55 (1H, dd), 3.56 (1H,m), 2.69 (5H,m), 1.80 (1H,m), 1.59 (2H, m), 1.30 (9H,s), 1.17 (2H,m), 0.78 (3H, t), 0.63 (3H, dd); MS (DCI/NH3) m/e 549.7 [M+H]+.

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The state of the s Example 37 (1) HV. U

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hvdroxy-N-[1'-isopropyl-1'-(4-((1RS)-1-hvdroxyethyl)imidazol-2-v1) lmethyl-6-phenyl-2-phenylmethyl-hexanamide

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The t-butyldimethylsiloxy-protected alcohol from Example 30(e) (20 mg, 1.0 eq) was stirred in anhydrous THF under an argon atmosphere at room temperature. Tetrabutyl ammonium fluoride (0.33 mL of a 1.0M solution in THF, 6.0 eq) was added and the solution stirred for 16 h. The solution was diluted with water and extracted with dichloromethane. combined organic extracts were washed with water and evaporated to a white solid. The solid was covered with diethyl ether and decanted twice to give the title compound makes white solid. (0.012) g, 72% (0.012) NMR (CDCl₃) δ 7.22-6.84 (10H, m), 6.61 (1H, s) $\frac{1}{2}$ 5.42 (1H, d) $\frac{1}{2}$ 4.69% (1H, m) $\frac{1}{2}$ 4.41 (1H, d), 3.58 (1H, m), 3.45 (1H, m), 2.78-2.40 (5H, m), 1.91 (1H, 3£20 m), 1.59 (2H, m), 1.41 (3H, d), 1.26 (9H, 7s) (rotamers) observed), 0.71 (3H, d), 0.59 (3H, dd); MS m/e 579.2 [M+H]+. end of the contract of the con

in the little of the property of the property

250 Preparation of (2R.48.58.1'S) -5-(191-dimethyl-2-88) hydroxyethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'imidazol-2-vl)methvl-6-phenvl-2-phenvlmethvl-hexanamide

a) 2-t-butyldimethylsiloxy-1,1-dimethylethyl-(4- 45) nitrophenyl) carbonate to property of the state of the st 30

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A mixture containing bis (4-nitrophenyl) carbonate (0.996 g, 3.28 mmol); 2-t-butyldimethylsiloxy-1;1-4 dimethylethanol (0.67 g, 1 eq) and 4-dimethylaminopyridine (0.4 g, 1 eq) in dichloromethane (50 mL) was stirred at room temperature for 5 d. The mixture was diluted with dichloromethane and washed successively with H2O and saturated aqueous NaCl, and dried over Na2CO36# The solvent was removed in vacuo, and the residue was purified by flash

chromatography (silica, 20% ethyl acetat /hexanes) to afford the title compound (35%). NMR(CDCl₃) & 8.25 (2H, m), 7.35 (2H, m), 3.76 (2H, s), 1.53 (6H, s), 0.94 (9H, s), 0.09 (6H, s).

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- b) (2R,4S,5S,1'S)-5-(2-t-butyldimethylsiloxy-1,1-dimethyl-ethoxycarbonyl)amino-4-t-butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide
- A solution of 2-t-butyldimethylsiloxy-1,1-dimethylethyl4-nitrophenyl carbonate (137 mg, 0.372 mmol), (2R,4S,5S,1'S)5-amino-4-t-butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide (102 mg, 0.186
 (100mm) and DMAP (45 mg, 0.372 mmol) in methylene choride was
 stirred at 20°C under Ar for 24 h. The solution was washed
- with aqueous Na₂CO₃, dried over solid Na₂CO₃ and concentrated.

 Flash chromatography (4% methanol/dichloromethane) provided

 the intermediate (2R, 4S, 5S, 1'S)-5-(2-t-butyldimethylsiloxy
 1, 1-dimethylethoxycarbonyl) amino-4-t-butyldimethylsiloxy-N
 (1'-isopropyl-1'-(1-(2-t-butyldimethylsiloxy-1, 1
 - dimethylethoxycarbonyl) imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide, which was dissolved in ether, washed with 10% NaOH, dried over Na₂CO₃, and concentrated to provide the title compound (110 mg, 78% overall). NMR(CDCl₃) δ 7.37-6.70 (13H, m), 6.39 (1H, d), 4.84 (1H, d), 4.55 (1H, t), 3.96 (1H, q), 3.69 (2H, s), 3.60-3.42 (2H, m), 2.94 (1H, s(br)), 2.85-2.44 (4H, m), 2.39 (1H, q), 1.90-1.60 (2H, m), 1.31 (6H, d), 1.02-0.85 (18H, m), 0.83 (6H, t), 0.98 (12H, m).
- c) (2R, 4S, 5S, 1'S)-5-(1, 1-dimethyl-2-hydroxyethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2yl) methyl-6-phenyl-2-phenylmethyl-hexanamide

mg) and tetra-n-butylammonium fluoride (6 eq of 1M solution in THF) under an argon atmosphere was allowed to stir at room temperature overnight. The solution was diluted with dichloromethane and washed with water, and the organic layer was concentrated. The residue was purified by flash chromatography (4% methanol/dichloromethane) to afford the

title compound (0.05 g, 66%). NMR (CDC13, CD3OD) δ 7.30-6.78 (12H, m), 4.42 (1H, d), 3.75-3.38 (4H, m), 2.97-2.50 (5H, m), 2.08 (1H, m), 1.70-1.56 (2H, m), 1.30 (6H, s), 0.90-0.55 (6H, dd).

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Example 39

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Preparation of (2R.4S.5S.1'S)=5-(1-1-dimethyl=2-hydroxy-ethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide hydrochloride

A 1M solution of HCl in ether (63.5 mL) was added to a solution of the compound of Example 38(c) (35 mg, 0.064 mmol) in methanol (5 mL). The solvent was removed by rotary evaporation at 20°C, and the solid residue was triturated with ether and dried to afford the title compound as the hydrochloride salt (35 mg, 95%). NMR(CD3OD) & 7:37-6.85 (12H, m), 4.56 (1H, d), 3.59 (1H, m), 3.48-3.33 (3H, m), 2.85-2.48 (6H, m), 2.04 (1H, septet), 1.72-1.49 (2H, m), 1.22 (6H, d), 0.88(3H, d), 0.61 (3H, dd).

Example 40 Post of district

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Preparation of (2R.4S.5S.1'S) -5-(2-hydroxyethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6phenyl-2-phenylmethylhexanamide

a) benzyloxyethyl-(4-nitro)phenylcarbonate

To a solution of 2-benzyloxyethanol (2.5 g, 16.4 mmol) and bis (4-nitrophenyl) carbonate (5.0 g, 1 eq) in dichloromethane (200 mL), N-methylmorpholine (1.81 mL, 1 eq) was added. The resulting mixture was allowed to stir at room temperature for 3 d. The reaction mixture was washed successively with H₂O and saturated aqueous NaCl and dried over Na₂SO₄. The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica, 20% ethyl acetate/hexanes) to afford the title compound (4.38 g,

- (m = 15.) 84%). 36NMR (CDCl₃) δ 8.26 (2H, m), 7.34 (7H, m), 4.62 (2H, s), 4.49 (2H, t), 3.70 (2H, t).
- b) (2R, 4S, 5S, 1'S) -5-(2-benzyloxyethoxycarbonyl) amino-4-t
 butyldimethylsiloxy-N-[1'-isopropyl-1'-(N'-(2-benzyloxyethoxy) carbonyl) imidazol-2-yl]methyl-6-phenyl-2
 phenylmethyl-hexanamide

To a solution of (2R, 4S, 5S, 1'S) -5-amino-4-tbutyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide (134.5 mg, 0.24 mmol) in dichloromethane (40 mL) under an argon atmosphere, benzyloxyethyl 4-nitrophenyl carbonate (160 mg, 2 eq) and 4dimethylaminopyridine (60 mg, 2 eq) were added. resulting mixture was allowed to stir at room temperature overnight, and was diluted with dichloromethane. The organic extract was washed successively with aqueous Na₂CO₃, H₂O, aqueous Na₂CO₃ and H₂O, and dried over Na₂CO₃. The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica, 4% methanol/dichloromethane) to afford the title compound (180 mg, 82%). NMR (CDCl₃) δ 7.45-6.80 (22H, m), 6.62 (1H, d), 5.60 (1H, t), 5.06 (1H, d), 4.60 (2H, s), 4.52 (2H, s), 4.50 (2H, m), 4.31 (1H, m), 4.07 (2H, m), 3.80 (2H, t), 3.68 (1H, q), 3.57 (1H, q), 2.85 (1H, m), 2.77-2.41 (4H, m), 2.09 (1H, m), 1.90 (1H, m), 1.73 (1H, m),

c) (2R,4S,5S,1'S)-5-(2-hydroxyethoxycarbonyl)amino-4-t-butyl-dimethylsiloxy-N-[1'-isopropyl-1'-(N'-2-benzyloxyethoxy-carbonyl)imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide

0.95 (9H, s), 0.81 (6H, dd), 0.11 (6H, d).

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The compound of Example 40(b) (68 mg, 0.44 mmol) was stirred as a solution in methanol (50 mL) with Pd(0) (10 mg) under 1 atm hydrogen for 12 h. The mixture was filtered, the solvent was removed in vacuo, and the residue was purified by flash chromatography (silica, 4% methanol/dichloromethane) to afford the title compound (44 mg, 74%). NMR(CDCl₃) & 7.36-6.72 (12H, m), 5.03 (1H, d), 4.80 (1H, dd), 4.50-4.32 (2H,

m), 4.07-3.52 (5H, m), 2.96-2.32 (6H, m), 1.98-1.85 (2H, m), 0.95 (9H, s), 0.90-0.75 (6H, dd), 0.05 (6H, d).

d) (2R,4S,5S,1'S)-5-(2-hydroxyethoxycarbonyl)amino-4-hydroxy5 N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide

To a solution of the compound of of Example 40(c) in methanol, excess aqueous HCl (approx. 5 equiv.) was added. The resulting solution was stirred at room temperature overnight, and concentrated under reduced pressure. The residue was diluted with H₂O, and made basic with aqueous Na₂CO₃. The mixture was extracted with dichloromethane, and the combined organic extracts were dried over Na₂CO₃. The solvent was removed in vacuo, and the residue was purified by flash chromatography to afford the title compound.

NMR(CD₃OD) δ 7.28-6.85 (12H, m), 4.55 (1H, d), 3.95 (1H, m), 3.73-3.40 (4H, m), 2.86-2.47 (5H, m), 1.99 (1H, m), 1.71 (1H, m), 1.22 (1H, m), 0.84 (3H, d), 0.62 (3H, d).

Example 41 state and backles

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hydroxyethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide

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a) 2-t-butyldimethylsiloxy-1-methylethyl-(4-nitrophenyl)-carbonate

A mixture containing bis (4-nitrophenyl) carbonate (3.20 g, 10.5 mmol), 2-t-butyldimethylsiloxy-1-methylethanol (2.0 g, 10.5 mmol) and 4-dimethylaminopyridine (1.30 g, 1 0.5 mmol) in dichloromethane (200 mL) was stirred at room temperature for 5 d. The mixture was then diluted with dichloromethane and washed successively with H₂O and saturated aqueous NaCl and dried over Na₂CO₃. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography (silica, 10% ethyl acetate/hexane) to afford the title compound (88%). NMR(CDCl₃) δ 8.28 (2H, m), 7.39

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3 \approx x.(2H, m)_{x/4}.98_{x}(1H, m)_{x} 3.75_{x}(2H, d)_{x/2}1.38_{x}(3H, s)_{x} 0.92_{x}(9H, s)_{x}
instros (Hs), O.11a(6H, As). The constitution of the most
                 BEST OF BUILDING OWN STREET
         sale ab) (2R, 4S, 5S, 1'S) -5-(2+t-butyldimethylsiloxy-1-methyl-
            5 ethoxycarbonyl)amino-4-t-butyldimethylsiloxy-N-(1'-isopropyl-
                   1'-imidazol-2-y1)methyl-6-phenyl-2-phenylmethyl-hexanamide
               Following the procedure of Example 38(b), except
                   substituting the compound of Example: 4(a) for 2-t-
 3 3 3 butyldimethylsiloxy-1,1-dimethylethyl-4-nitrophenyl
       $\, 10 \cappa_carbonate, \(\)the title \(\)compound \(\)was \(\)prepared. \(\) NMR (CDCl3) \delta
  조로 하다 1.40-7.00 (10H, m), 6.90 (1/2H, es), 6.72-(1/2H, s), 6.45 (1H,
       30 sales dd), 34.92 0(1H, add); 4.84-4.61 (2H, m), 4.10 (1H, m), 3.76
 braining vo(1H, m), 23.58 (1H, m), 2.92-2.73 (3H, m), 2.70-2.45 (3H, m),
    1.78 (2H, m), 1.22-1.08 (3H, m), 1.04-0.81 (24H, m), 0.17-
   15/ 15/ 10:00 (12H, m)t. 2001 and a control of the first with the control of
                     how a coor in . The and due ear interested with
      287 246c) [(2R, 4S, 5S, 1'S) -5-((1RS) -1-methyl-2-hydroxyethoxycarbonyl) - ...
     YANG Tamino-4-hydroxy-N-(1"-isopropyl-1'-imidazol-2-yl) methyl-6-
               Dephenyl-2-phenylmethyl-hexanamide and the control of the control 
          20
                            Following the procedure of Example 38(c), except using
                  the compound of Example 4(b), the title compound is prepared.
                -MR(CD_3OD): \delta/7.15-6.68/(12H_{\star}) m), 1.5.72-5.60 (1H, dd), 4.58
  -- 1 -- 1 (1H, m), 4.38 (1H, add); 4.06 (1H, m), 3.62 ((1H, m), 3.41 (1H,
    · (1H, dd), 2.79-2.55 ((5H, 7m)), 2.49: (1H, dd), 1.92 (1H, m), 1.67 (1H,
        -25 m), 1.08-0.98 +(3H,-dd); +0.69 +(3H,-dd), +(0.58) +(3H,-dd). +1
     this few himsers the community of the contract of the contract of
      -Lyddeni'ydieir - Y-fym - ta-Berydaeni Example 42 bin - te Tyr Sare E
    (Commatted and Carlo Hell Morning that the form of the contraction
       nd ( Preparation of (2R.4S.5S.1'S) -5-(2-hydroxy-1- d) fee
      esi30 cyclopentyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-
      hadasimidazol-2-vl)methyl-6-phenyl-2-phenylmethylhexanamide
       wind and the end of the action blooming the slutching and
              esa) 3 (trans) -2-(t-butyldimethysiloxy) -cyclopentanol ca
    oubteen will Torasmixture of t-butyldimethylsilyl chloride (5.08 g,
                 33.7 mmol) and imidazole (2.30 g, 33.7 mmol) in DMF (10 mL),
    as solution of trans-1,2-cyclopentanediol in DMF (4 mL) was
                 added. The reaction mixture was stirred overnight at 25°C.
                 The r action mixture was dilut d with ice water and extracted
```

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with ether. The ether extract was washed with water and brine, dried over magnesium sulfate, filtered and the solvent removed in vacuo. The residue was purified by flash chromatography (silica, 9:1 hexane:ethyleacetate) to the

nitrophenyl) carbonate () an oppose of a saturate of

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To a solution of the compound of Example 42(a) (1.08 g, 5 mmol) and DMAP (0.611 g, 5 mmol) in dichloromethane (12 mL), bis (4-nitrophenyl) carbonate (1.52 g, 5 mmol) was added. The solution was stirred overnight at 25°C. The reaction mixture was diluted with dichloromethane (15 mL), and washed with water and brine. The organic extract was dried over 15 magnesium sulfate, filtered, and the solvent was removed at reduced pressure. The residue was triturated with hexane:ethyl acetate (1:1) and filtered. The filtrate was evaporated to an oil and purified by flash chromatography (silica, 9:1 hexane:ethyl acetate) to yield the title compound as an oil (1.75 g, 92%).

c) 5-((trans)-2-t-butyldimethylsiloxy-cyclopentyloxy-carbonyl) amino-4-t-butyldimethysiloxy-N-[1'-isopropyl-1'-(1-(2-t-butyldimethysiloxy-cyclopentyloxycarbonyl)) imidazol-225 (yl]methyl-6-phenyl-2-phenylmethyl-hexanamide

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A solution of 5-amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide (171 mg, 0.311 mmol), DMAP (76.1 mg, 0.623 mmol) and the compound of Example 42(b) (238 mg, 0.623 mmol) in dichloromethane (9 mL) was stirred overnight at 25°C. The reaction mixture was diluted with dichloromethane, washed with water and saturated sodium bicarbonate solution, and dried with magnesium sulfate. The organic extract was filtered and the solvent was removed in vacuo. The residue was purified by flash chromatography (silica, 4:1 hexane:ethyl acetate) to yield the title compound as an oil (150 mg, 47%).

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ns jedd) 5-((trans)-2-hydroxy-cyclopentyloxycarbonyl) amino-4.30 hydroxy-N-[1'-isopropyl-1'-imidazol-2-yl]methyl-6-phenyl-2manage phenylmethyl-hexanamide;

To a solution of the compound of Example 42(c) (150 mg, 0.145 mmol) in methanol (5 mL), 3N HCl (3 mL) was added. The solution was stirred overnight at 25°C. The methanol was evaporated in vacuo, and the residue was diluted with water and extracted with ether. The aqueous solution was neutralized with 5% sodium carbonate (~pH 7) and a solid field (precipitated. The solid was filtered, washed with water and dried in vacuo to yield the title compound (51.5 mg, 63%).

NMR(CD3OD, 400 MHz), 8.7.0-7.3 (m, 10H), 6.87 (s, 2H), 4.63 (field (m, 2H), 3.88 (m, 1H), 3.55 (d, 1H), 2.5-2.9 m, 5H), 1.4-2.1 (br, 9H), 0.88 (d, 3H), 0.71 (d, 3H); TLC Rf 0.27 (silica, 8% methanol/chloroform).

bor (korrediki dis er eg sidsmy o o Example 43 musdangus bija .

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-11) - A-Lindings of coales (In that the Co. 144) - A- 25 (46.05 (48)) (1)

a) t-butyldimethylsilyl 4-(t-butyldimethylsiloxy)-butanoate

To a suspension of t-butyldimethylsilyl-chloride (29.9

25a (g,)198)mmol)cin.dry.DMF (20 mL), 4-hydroxybutyric acid,

88.S. As sodium salts (5.0 g, 397 mmol) and imidazole (27.0 g, 0.397 mol)n were added. The reaction mixture was stirred overnight

at 25°C. The solvent was removed under reduced pressure and

the residue was diluted with 10% aqueous citric acid (200

30 mL). The residue was extracted with ether. The ether

(30 solution was dried with magnesium sulfate, filtered and

(30 solution was dried with magnesium sulfate, filtered and

(30 solution was dried with magnesium sulfate, filtered and

10 (17) 7.6-13 (m) OP: 6.86 (s, 27), 6.46 (4, 11), 1.66

(b) 4-t-butyldimethylsiloxy-butanoic acid

(A) solution of the compound of Example 43(a) (5.0 g) was

(dissolved in acetic acid:tetrahydrofuran:water (2:2:1, 50 mL)

solution and stirred for 2.5 h. The solution was diluted

with water and extracted with ether. The ether solution was

dried with magnesium sulfate, filtered and evaporated to an oil. The oil was purified by flash chromatography (silica, hexane-ethyl acetate, 9:1) to yield the title compound as an oil (180 mg).

c) (2R, 4S, 5S, 1'S) -5-(4-t-butyldimethylsiloxy-butanoyl) amino4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2phenylmethylhexanamide (1) 1986 4 10 1030 587 \$20 butanoyl)

A solution of (2R,4S,5S,1'S)-5-amino-4-t
butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl6-phenyl-2-phenylmethyl-hexanamide (175 mg, 0.319 mmol), 4-tbutyldimethylsiloxy-butanoic acid (84 mg, 0.41 mmol), BOP
reagent (148, 0.335 mmol), triethylamine (46 µL, 0;335 mmol)
and dichloromethane (4 mL) were stirred at 20°C under Ar for
15 24 h. The reaction mixture was diluted with dichloromethane,
washed with aqueous Na₂CO₃, water and brine, and dried over
solid magnesium sulfate. The organic phase was filtered, and
concentrated in vacuo. The residue was purified by flash
chromatography (silica, 2% methanol/chloroform) to provide
the title compound.

d) (2R, 4S, 5S, 1'S) -5-(4-hydroxybutanoyl) amino-4-hydroxy-N-(1'9:000 isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-36-0 is
0:000 ophenylmethylhexanamide of to not have a so

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- A solution of the compound of Example 43 (c) (177 mg, 0.236 mmol) and tetra-n-butylammonium fluoride (2.84 mL, 2.84 mmol, 1M solution in THF) was stirred under an argon atmosphere at room temperature overnight. The solution was diluted with ethyl acetate, washed with saturated sodium bicarbonate solution, and water, and the organic layer was concentrated. The residue was precipitated from the ethyl acetate solution to afford the title compound: NMR δ (CD3OD, 400 MHz) 7.0-7.3 (m, 10H), 6.86 (s, 2H), 4.62 (d, 1H), 4.05 (m, 1H), 3.43 (t, 2H), 2.55-2.90 (m, 4H), 2.60 (m, 1H), 2.17
 - 35 (m, 2H), 2.05 (m, 1H), 1.76 (m, 1H), 1.67 (m, 2H), 1.55 (m, 1H), .88 (d, 3H), .72 (d, 3H); TLC R_f 0.40 (silica, 10% methanol/chloroform).

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Berningson Example 44

Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(benzyloxycarbonyl) valylamino-6-phenyl-N-(1'-isobutyl-1'-imidazo-2-yl) methyl-hexanamide

- (a) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-butyldimethylsiloxy-5-(benzyloxycarbonyl) valylamino-6-phenyl-N-(1'-isobutyl-1'-(imidazo-2-yl)) methyl-hexanamide.
- A solution of carbobenzyloxy-(L)-valine (50.4 mg, 0.20 mmol), the product of Example 13(a) (110 mg, 0.20 mmol), BOP (88.7 mg, 0.20 mmol) and triethylamine (28 μl, 0.20 mmol) in methylene chloride (4 mL) was stirred at 25°C for 4 dd. The reaction mixture was diluted with methylene chloride, 15° washed with saturated sodium bicarbonate and the organic layer was concentrated. The product was purified by flash chromatography (silica gel, 4% CH2Cl2/ MeOH) to give the stitle compound (104 mg, 67%).
 - imidazo-2-yl) methyl-hexanamide.

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To a solution of the compound of Example 44(a) (104 mg, 0.133 mmol) in MeOH (8 mL), 3N HCl (2 mL) was added. The 25°C solution was stirred for 16 hrs at 25°C. The methanol was removed at reduced pressure and 10% sodium carbonate was added to pH ~7.5. Ether (10 mL) was added and the solid invibit product was filtered and dried in vacuo to provide the title for [coscompound (58 mg, 65%). NMR(CDCl3) & 0.62 (d, 3H), 0.78 (d, 10.301) 3H), 0.82 (d, 3H), 0.90 (d, 3H), 1.62 (m, 2H), 1.96 (m, 1H), add 2.06 (m, 1H), 2.55 (m, 1H), 2.77 (m, 4H), 3.38 (s, 1H), 3.53 (section of the compound (5.8 mg, 6.85 (s, 2H), 6.92-7.34 (m, 15H); 0.41 (m, 15H); 6.85 (s, 2H), 6.92-7.34 (m, 15H);

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Example 45

Preparation of (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(N-acetylvalyl) amino-6-phenyl-N-(1'-isobutyl-1'-imidazo-2-

- 5 <u>vl) methyl-hexanamide Chicketta thiyedance kilasis dalla v</u>
- (a) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-t-butŷldimethylsil) oxy-5-(N-acetyl-valyl) amino-6-phenyl-N-(1'-isobutyl-1'-imidazo-2-yl) methyl-hexanamide
- mmol) in dry THF (8 mL) at -40°C was added n-methylmorpholine (55.7 μl, 0.506 mmol) followed by isobutyl chloroformate (33.5 μl, 0.253 mmol). The reaction mixture was stirred for 15 min, and the compound of Example 13(b) (139 mg, 0.253 mmol) in THF (3 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 2 d. The reaction was diluted with ethyl acetate, and washed with water and brine. The organic solution was dried with sodium sulfate, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography (silica, 4% methanol/chloroform) to give the product as an oil (47 mg, 27%).
 - (b) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(N-L) (N-L) (N-L

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To a solution of the compound of Example 45(a) (47 mg, 0.0681 mmol) in methanol (3 mL), 3N HCl (0.5 mL) was added. The reaction was stirred for 16 h at 25°C. The methanol was removed under reduced pressure and the solution was diluted with water and neutralized with 5% sodium carbonate. The solid product was filtered, washed with water and ether, and dried in vacuo to yield the title compound (29.5 mg, (75%). NMR (CD3OD) & 0.70 (d, 3H), 0.88 (m, 9H), 1.57 (m, 1H), 1.70 (m, 1H), 1.92 (s, 3H), 2.05 (m, 1H), 2.55 (q, 1H), 2.77 (m, 4H), 3.57 (d, 1H), 4.03 (m, 2H), 4.60 (d, 1H), 6.87 (s, 2H),

6.95-6.20 (m, 10H); MS m/e 575 [M+H]⁺.

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Bodow tampids up wow of tobre police Example: 46 consist (a consis
    boutcideso on which is hipportal by so it is a marrogen of a se-
             #6 (Preparation of (2R,4S,5S,1'S)-5-[(imidazol-2-
             yl)methyloxycarbonyllamino-4-hydroxy-N-(1'-isopropyl-1'-
       5 imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide
 value for the first of the same the care of the better the contract the
 AM 「中央 a)は(1-(benzyloxymethyl) imidazol-2-yl) methyl-(4-())
  29.0 (F nitrophenyl) carbonate( 5) (0.0 (0.0 cm (0.1 cm))
 1 (1-18) A mixture of bis (4-nitrophenyl) carbonate, (1-
                   benzyloxymethyl)imidazol-2-yl)methanol and 4-
  hand and dimethylaminopyridine was areacted according to the procedure
    The type of Example 14(a) to afford the title compound (58%).
                   NMR (CDCl<sub>3</sub>, 400 MHz) \delta 8.18 (d, 2 H, J=8.38 Hz), 7.44-7.23 (m,
    後20 (6) 87H)(-7.11水(s, 1H)(-17.13以(s, 1H))、5.48 (s, 2H), 5.44 (s, 2H),
    000.15 (4.49 (s. 2H) 1000 minutes can a city (but) since an expec-
may elve attempt as 1990 for 20 at 17m solution and the cold the
   (1-benzyloxymethyl) imidazol-2-
    # 10 % actively methyloxycarbonyl) amino-4-t-butyldimethylsiloxy-N-(1'-
    ########isopropyl-1!-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
      a " 20 (hexanamide) basegues of the four fiberals with a fire gas
    The A mixture of the compound of Example 46(a), 10
 、(注意 、m) ②(2R,4S)5S,1!S)-5-amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-
  28 de (GLI2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide, and 4-
   dimethylaminopyridine was reacted according to the procedure
                   of Example 14(b) to afford the title compound (32%).
      NMR (CDCl<sub>3</sub>) \delta 7.50-6.60 (m, 19H), 5.25 (m, 2H), 5.11 (d, 2H,
                   J=11.03 Hz), 4.68 (m, 1H), 4.39 (m, 2H), 3.97 (m, 1H), 3.67
                   (m, 1H), 2.88 (m, 1H), 2.72-2.28 (m, 6H), 1.85 (m, 1H), 1.60
companies (m, 1H), 0.92-0.818 (m, 15H), 0.807 (s, 3H), 0.06 (s, 3H);
  about a ser exist in the first product of the series of th
                          (2R, 4S, 5S, 1'S)-5-(imidazoyl-2-yl-
                  methyloxycarbonyl) amino-4-t-butyldimethylsiloxy-N-(1'-
                   isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
    -1) 351 - hexanamide:outso (type://joxthin-b/jill File orlings) -
                   The compound of Example 46(b) (58 mg, 0.073 mmol),
   methanol (3 mL), and 10% Pd on carbon (50 mg) were combined
```

and stirred under 1 atm of H2 for 24 h. Additional catalyst

(50 mg) was added and stirring under H₂ was continued for 8 h. The reaction was filtered through Celite®, concentrated and flash chromatographed (silica, step gradient, 0-8% MeOH/CH₂Cl₂) to yield the title compound (28 mg, 57%).

5 NMR (CDCl₃) δ 7.29-6.83 (m, 14H); 5.05 (d, 1H, J=11.2 Hz), 4.91 (d, 1H, J=11.2 Hz), 4.71 (m, 1H), 3.92 (m, 1H), 3.61 (m, 1H), 3.02 (m, 1H), 2.81-2.54 (m, 4H), 2.36 (m, 1H), 1.93 (m, 1H), 1.59 (m, 1H), 0.91 (d, 3H, J=7.1 Hz), 0.89 (s, 9), 0.69 (d, 3H, J=7.1 Hz), 0.84-0.05 (m, 6H); MS (ES) m/e 673 [M+H]+.

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d) (2R, 4S, 5S, 1'S) -5-(imidazol-2-yl-methyloxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide 82 m i (xxxx 00 8 x 2 10 00 8 x 2 10

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The compound of Example 46(c) (24 mg, 0.035 mmoL), 95% aqueous EtOH (0.50 mL), and concentrated aqueous HCl (0.050 mL) were stirred at 23°C for 24 h. The solution was diluted with H2O (5 mL) washed with EtOAc and then the aqueous phase was made basic by addition of solid K2CO3. Extraction with EtOAc, concentration of the organic extract and trituration with CH2Cl2 afforded the title compound (14 mg, 72%). SNMR (CDCl3) δ 7.33-6.85 (m, 14H), 5.11 (d, 1H, J=10.8 Hz), 4.96 (d, 1H, J=10.8 Hz), 4.47 (m, 1H), 3.72 (m, 1H), 3.38 (m, 1H), 2.81 (m, 4H), 2.59 (m, 1H), 2.07 (m, 1H), 1.72 (m, 1H), 1.62 (m, 1H), 0.78 (d, 3H, J=6.63 Hz), 0.67 (d, 3H, J=6.63 Hz); (m, 6H); MS(ES) m/e 559 [M+H]⁺.

Example 47 . 6 . (23 80 87 5

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(N (a) 53.5 (M) 401

Preparation of (2R.4S.5S.1'S.1"RS)-5-((1"-(imidazol-2-yl)-2"methyl)propyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide

a) (1RS)-1-((1-benzyloxymethylimidazol-2-yl)-2-ir m methyl) propyl-(4-nitrophenyl) carbonate (1 fygo 100 km)

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A mixture of bis(4-nitrophenyl) carbonate (1RS)-1-((1-benzyloxymethylimidazol-2-yl)-2-m thyl) propanol and 4-dimethylaminopyridine was reacted according to the procedure of Example 14(a) to afford the title compound (61%). NMR

```
(CDCl<sub>3</sub>) δ 8.18 (d, 2H, J=8.31 Hz), 7.38-7.21 (m, 7H), 7.13

(s, 1H), 6.94 (s, 1H), 5.74 (d, 1H, J=11.1 Hz), 5.47 (d, 1H, J=10.2 Hz), 4.53 (d, 1H, J=11.3 Hz), 4.41 (d, 1H, J=11.3 Hz), 2.64 (m, 1H), 1.18 (d, 3H, J=6.02 Hz), 0.87 (d, 3H, J=6.02 Hz); MS(ES) m/e 426 [M+H]<sup>+</sup>.
```

- b) (2R, 4S, 5S, 1, S, 1, RS) -5-((1, -(1-benzyloxymethylimidazol-2y yl) -2, -methyl-propyl) oxycarbonyl) amino-4-tbutyldimethylsiloxy-N-(1, -isopropyl-1, -(1-(1, -(1-
 - 10 benzyloxymethylimidazol-2-yl)-2"-
- bination methylpropyl)oxycarbonyl)imidazol-2-yl)methyl-6-phenyl-2biophenylmethyl-hexanamidelloridadia
- mmol), the compound of Example 13(a) (75.9 mg, 0.14 mmol), 4
 15 Tdimethylaminopyridine (41 mg, 0.33 mmol) and DMF (0.5 mL) was

 stirred under argon for 18 h. The DMF was evaporated in

 vacuo and the residue was combined with 10% aq K2CO3 (10 mL)

 and extracted with EtOAc. The combined extracts were washed

 with saturated aq NaHCO3, dried (K2CO3), filtered and
 - 20 concentrated in vacuo. The residue was flash chromatographed in vacuo

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A solution of the compound of Example 47(b) (81 mg, 0.07 mg, mmol), CH3OH (0.75 mL), and 3N aqueous HCl (0.25 mL) was stirred at 23°C for 20 h. The reaction mixture was diluted with H2O (10 mL) and washed with EtOAc (3 x 15mL). Solid Example 47(b) was added to give a basic solution (pH>12), which was extracted with EtOAc. The extracts were dried (K2CO3), filtered, concentrated and flash chromatographed (silica, step gradient, 0-8% CH3OH/CH2Cl2) to give the title compound

(34.9 mg, 65%). ¹H NMR (CDCl₃) 8 7.43-6.79 (m, 9H), 5.87, 5.66 (2d, 1H, J=10.66, 10.85 Hz), 5.28 (m, 2H), 4.68 (m, 1H), 4.42 (m, 2H), 3.71 (m, 1H), 3.58 (m, 1H), 2.90-2.31 (m, 6H), 00 - 2.11 (m, 1H), 1.75, 1.51 (2m, 2H), 1.05, 0.97 (2d, 3H, J=6.32,6.45), 0.68 (m, 9H) 30 and (Here Exercise)

(2R,4S,5S,1'S,1"RS)-5-((1"-'(imidazol-2-yl)-2"methyl) propyloxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide.

A mixture of the compound of Example 47(c) (34 mg; under H2 (1 atm) for 26 h. The suspension was filtered through Celite®, concentrated, and triturated with CH2Cl2 to \sim 14%) yield the title compound (4 mg, 14%) \sim 14% (CDCl3/CD3OD) δ 15 (15 (7.7.32-6.71 (m, 14H), 15.38 (m, 1H), 4.55 (m, 1H), 13:72 (m, 1H), 3.55 (m, 1H), 2.78 (m, 4H), 2.55 (m, 1H), 2.15 (m, 2H), (iii) 1.60 (m, 2H), 1.03-0.61 (m, 12H). Ber with this proper

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Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hvdroxy-N-[1'-isopropyl-1'-(4-(imidazol-2-vl)imidazol-2vi) lmethyl-6-phenyl-2-phenylmethyl-hexanamide(a) Control of the contro

(a) (1'S)-1'-(carbobenzyloxy) amino-1'-isopropyl-1'-(4- is 25 (imidazol-2-yl) imidazol-2-yl) methane

Cbz-(L)-valinal (0.45 g, 1.4 mmol) was stirred in anhydrous methanol at 0°C under argon. (Glyoxal (40% in water) (0.22 mL, 1.4 mmol) and ammonium hydroxide (29% NH3) (0.88 mL, 14 mmol) were added and the mixture was allowed to stir at 0°C for 1 h. The cooling bath was removed and the solution stirred at room temperature for 16 h. The methanol was evaporated in vacuo and the residue was diluted with 5% aqueous HCl. After extracting with dichloromethane, the aqueous layer was made basic with solid sodium carbonate and extracted with dichloromethane. The combined organic extracts were dried over sodium carbonate, filtered, and evaporated to a solid which was chromatographed (silica, 4%

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methanol/dichlorom thane) to give th title compound (0.216 g, 43%) as a white solid. NMR (CDCl3) δ 7.15 (6H, s(br)), 6.88 (2H, s), 6.30 (1H, d), 4.89 (2H, dd), 4.52 (1H, t), 2.05 (1H, m), 0.73 (3H, d), 0.62 (3H, d). MS m/e 340.2 [M+H]+

(b) (2R, 4S, 5S, 1'S)-5-(t-butoxycarbonyl) amino-4-hydroxy-N[1'-isopropyl-1'-(4-(imidazol-2-yl) imidazol-2-yl)] methyl-6phenyl-2-phenylmethyl-hexanamide

The compound of Example 48(a) (0.13 gm.) was dissolved in anhydrous methanol with 10% Pd on activated carbon (0.02 g). Hydrogen gas was bubbled through the solution via balloon for 1 h and the solution was stirred overnight under a hydrogen atmosphere. The mixture was filtered through a pad of Celite® and evaporated to yield 1'-amino-1'-isopropyl-15 [4-(imidazol-2-yl)imidazol-2-yl]methane as a white solid (0.13 g, 100%).

This compound was combined with the compound of Example 13(a) (0.334 g, 0.63 mmol), BOP reagent (0.28 g, 0.63 mmol), and triethylamine (0.13 mL, 0.945 mmol) in DMF (1 mL) and allowed to stir under Ar for 3 d. The DMF was evaporated in vacuo and the residue was diluted with dichloromethane. The solution was washed with water and brine. The organic layer was dried over sodium carbonate, filtered, and evaporated to yield (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethysiloxy-N-[1'-isopropyl-1'-(4-(imidazol-2-yl) imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl; hexanamide as

A portion of the solid (0.100 g, 0.14 mmol) was stirred in THF at room temperature under argon. Tetrabutylammonium fluoride (0.84 mL, 0.84 mmol) was added and the mixture was allowed to stir for 16 h. The solution was diluted with water and extracted twice with dichloromethane. The combined organic extracts were washed with water and evaporated to an oily residue. The residue was dissolved in THF and several drops of diethyl ether were added until a white precipitate formed. The precipitate was collected by filtration and dried in vacuo to yield the titl compound as a white solid (76 mg, 90%). NMR (CD3OD) & 7.37-6.84 (13H, m), 4.61 (1H,

· fwittona white solid. A large of the a provided the standard

d), 3.69 (2H, m), 3.54 (1H, d), 2.84-2.52 (5H, m), 2.06 (1H, m), 1.83 (2H, m), 1.57 (1H, m), 1.30 (9H, s), 0.87 (3H, d), 0.69 (3H, d); MS m/e 601.2 [M+H]+ UE.3 (6 ,ES)

Example 49

A STATE OF THE STATE OF THE STATE OF

Preparation of (2R:4S:5S:1'S)-5-[di(hydroxymethyl)methoxycarbonyllamino-4-hydroxy-N-(1'-isopropyl-1'-imidazol 2-vl) methyl-6-phenýl-2-phenýlmethýl-hexanamide 10 and the contract of the contract of the contraction of the contract

a) di(t-butyldimethylsiloxymethyl) methyl-(4-nitrophenyl) the real Community of the second and the contraction of the contractio carbonate

A mixture containing bis (4-nitrophenyl) carbonate (1.89 g, 6.21 mmol), di (t-butyldimethylsiloxymethyl) methanol (2.00

- 15 q, 1 eq) and 4-dimethylaminopyridine (757 mg, 1 eq) in dichloromethane (100 mL) was stirred at room temperature for 2 d. The mixture was diluted with dichloromethane and washed with saturated aqueous Na₂CO₃, brine, and dried over Na₂SO₄. The solvent was removed in vacuo, 0 and the residue was
- es 20 purified by flash chromatography (silica, 10% ethylis max ... acetate/hexanes) to afford the title compound (75%) "NMR $\delta = 8.29 \cdot (2H/6m)/67.37 \cdot (2H/6m)/63/966 \cdot (1H/6m)/63.85$ (2H, d), 3.82 (2H, d), 0.89 (18H, s) 7 0.09 (12H, s)
- b) (2R, 4S, 5S, 1'S) -5- (di (t- / 1) I) Mingle Sillings (Write Syrad) 80 butyldimethylsiloxymethyl) methyloxycarbonyl amino-4-tbutyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methylb as a 6-phenyl-2-phenylmethyl-hexanamide b b northbo A

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A solution of di(t-butyldimethylsiloxymethyl)-methyl 4-30 nitrophenyl carbonate (475 mg, 0.974 mmol), the compound of Example 13(a) (178 mg, 0.325 mmol) and dimethylaminopyridine (119 mg, 0.974 mmol) in methylene choride was stirred at 20°C under Ar for 24 h. The solution was washed with aqueous Na₂CO₃, dried over solid Na₂CO₃ and concentrated in vacuo.

35 Flash chromatography (silica, 4% methanol/dichloromethane) of the residue provided the intermediate (2R, 4S, 5S, 1'S) -5-(di(tbutyldimethylsiloxymethyl) methyloxycarbonyl)amino-4-tbutyldimethylsiloxy-N-(1'-isopropyl-1'-(1-(di(tbutyldimethylsiloxym thyl) methyloxycarbonyl) imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide, which was dissolved in ether, washed with 10% NaOH, dried over Na₂CO₃, and concentrated to provide the title compound (197 mg, 71%).

5 NMR (CDCl₃) & 7.43-7.05 (10H, m), 6.90 (2H, s), 6.65 (1H, bs), 5.09 (1H, d), 4.78 (1H, bd), 4.08 (1H, m), 3.89-3.50 (7H,m) 3.00-2.80 (4H, m), 2.65 (1H, m), 2.55 (2H, m), 1.90 (1H, m), 1.78 (1H, m), 1.10-0.85 (33H, m), 0.20-0.06 (18H, m).

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c) (2R, 4S, 5S, 1'S) -5- (di (hydroxymethyl) methoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2phenylmethyl-hexanamide

A mixture containing the compound of Example 49(b) (50

15 mg) and ethereal HCl (4 eq) was allowed to stir in
methanol:water (9:1) at room temperature overnight. The
solvent was removed in vacuo, and the residue was diluted
with ethyl acetate and washed with saturated aqueous Na₂CO₃.

The product was purified by flash chromatography (silica, 4%

20 methanol/dichloromethane) to afford the title compound
(29 mg, 94%). NMR (CD₃OD) & 7.20-6.80 (10H, m), 6.71 (2H,
s), -4.50 (1H, d), 3.90 (1H, m), 3.65-3.34 (5H, m), 2.82-2.45
(6H, m), 1.99 (1H, m), 1.74 (1H, m), 1.52 (1H, m), 0.78 (3H,
d), 0.60 (3H, d).

en Janimann an 424 - John en of de la <mark>Example 50</mark> y 1981 and 1991 and

Preparation of (2R.4S.5S.1'S)-5-(1-oxo-thian-4-3)
yl)oxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-30, yl)methyl-6-phenyl-2-phenylmethylhexanamide
Reacting the compound of Example 32(b) (81 mg, .133 mmol)
with m-chloro perbenzoic acid (23 mg, 0.133 mmol) in CH2Cl2
yielded the title compound. NMR (CD3OD) & 7.20-6.85 (10H, m), (6.78 (2H, s), 4.51 (1H, d), 3.66 (1H, m), 3.42(1H, m), (35H3 2.95-2.41 (9H, m), 2.32-2.01 (2H, m), 1.99-1.63 (4H, m), (1.60-1.41 (2H, m), 2.0.78 (3H, d), 0.60 (3H, d); MS m/e 595.2 [M+H]+.

Example 51 44 persons and

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Preparation of (2R,4S,5S,1 S)=5-((tetrahydrosulfonvlpvran-4yl)oxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2yl) methyl-6-phenyl-2-phenylmethylhexanamide DOD A-48 2

Reacting the compound of Example 50 (31 mg, 49.2 mol) with m-chloro perbenzoic acid (10 mg, 59.2 mol), in methylene chloride yielded the title compound. NMR (CD3OD) δ 7.20-6.85 (10H, m), 6.76 (2H, s), 4.48 (1H, d), 3.68 (1H, m) 3.44 (1H, m), 2.96-2.42 (9H, m), 2.32-2.04 (2H, m), 1.97-1.62 (4H, m), 1.61-1.43 (2H, m), 0.79(3H, d), 0.60 (3H, d); MS m/e 611.2 Cornell Colored Consider 1) - Segmented & [M+H]+.

Example 52. Part of the control of t

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Preparation of (2R.4S.5S.1'S)-5-(1.1-dimethyl-2-idea) acetoxyethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'imidazol-2-vl)methyl-6-phenyl-2-phenylmethyl-hexanamide

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20% (a) 5:(2R, 4S, 5S, 1'S) -5-(1, 1-dimethyl-2-) 46 lb \ lagration 108 hydroxyethoxycarbonyl) amino-4-(t-butyldimethylsilyl) oxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide

The compound of Example 38(b) (223 mg, 0.221 mmol) was dissolved in 10% aqueous methanol and combined with 1M HCl in ether (0.221 mL, 1 eq) at room temperature. After completion of the reaction the solvents were removed in vacuo. The residue was dissolved in dichloromethane and washed with aqueous saturated Na2CO3. The organic layer was concentrated and the residue was purified by flash chromatography (silica, 4% methanol/dichloromethane) to provide the title compound (138 mg, 94%). NMR (CDCl3) $\delta = 7.38 - 6.81$ (12H, m), 4.4.93 + 4.65(1H, d, rotamers), 4.81+ 4.48 (1H, t, rotamers), 4.15 + 4.08 (1H,d, rotamers), 3.90 (1H,q), 3.72 (2H, m), 3.50+3.38 (1H, d, rotamers); 2.98-2.48 (5H, m), (2.35 (1H, m), 1.98 (1H, m), 1.79 (1H, m), 1.60 ((1H, m), 1.30 ((3h, s), 1.29 (3H,s), 1.09 -0.85 (15H, m), 0.79 (3H, d), 0.11 (6H, m).

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- (b) (2R, 4S, 5S, 1!S) 5 (1, 1 dimethyl 2 dimethyl 2 1 dimethyl 2 dimethyl 2 dimethyl 2 dimethyl 2 dimethyl 2 -
- 29) Surgacetoxyethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'Size (Simidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide
- b (E7) 88 5 The compound of Example 52(a) (103 mg, 0.155 mmol) was
- stirred with acetic anhydride (30 mg, 0.309 mmol) and DMAP (40 mg, 0.309 mmol) in methylene chloride at room temperature

the residue was flash chomatagraphed (silica, 4% methanol/dichloromethane).

- mg, 0.140 mmol) was stirred in methanol:water (9:1) with 1M HCl in ether (0.14 mL, 1 eq). The solvents were removed in water vacuo, the residue was diluted with dichloromethane, and the solution was washed with aqueous Na₂CO₃. The organic layer
- colling chromatography: (silica; 5% methanol/dichloromethane) to off; proprovide the title compound; (82 mg; 91%). NMR (CD3OD) & 7.29-
- 6.90 (10H, m), 6.81 (2H, s), 4.51 (1H, d), 4.05 (2H, s), 3.59 (1H, m), 3.42 (1H, m), 2.80-2.45 (5H, m), 2.00 (1H, m),
- (65 205) 1998 (3H, 8s), 1972 (1H, m), 1950 (1H, 8m), 1934 (6H, d); 0.81

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Example 53

- 25 Preparation of (2R.4S.5S.1'S)-5-((1.1-dimethyl-2-(benzyloxy-carbonylglycyloxy)ethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide hydrochloride salt
- a) (2R,4S,5S,1'S)-5-((1,1-dimethyl-2-maintenance) acarbobenzyloxyglycyloxy) ethoxycarbonyl) amino-4-(t-butyldimethylsilyloxy)-N-(1'-isopropyl-1'-imidazol-2-maintenance) (y1) methyl-6-phenyl-2-phenylmethyl-hexanamide

The compound of Example 52(a) (100 mg, 0.151 mmol) was reacted with 2-chloro-1-methyl-pyridium iodide (92 mg, 0.36 mmol), DMAP (75 mg, 0.60 mmol) and Cbz-glycine (63 mg, 0.30 mmol) in methylene chloride (5 mL) under argoniatire flux for

16.3 htt Solvents were removed in vacuo and the product was

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purified by flash chromatagraphy (silica 4%) (0) methanol/dichloromethane) nto provide the title compound (95 0.00 mg, 0.73). NMR (CDCl3) 0.00 0.0100 6.00 (1H,m), 5.20 (1H, m) 205.15 (2H; us) 204.830+ 4.55 (1H, d, 5 0 rotamers), 4.65+44.48 (1H,6t,6rotamers), 624v81e+24.38 (1H,q, 1.55 (1H, m), 1.38 (3h, s), 1.29 (3H, s), 01.90 (9H, m), 0.85 (3H, d), 0.70 (3H, d), 0.11 (6H; m) mos distriby Lorand tent with the second state of the profit east off. 10 行立 (1.1kx - b) (2R, 4S, 5S, 1'S) -5-((1, 1-dimethyl-2-(3.2kx) ()) 4. () () () () (benzyloxycarbonyl) ethoxycarbonyl) amino-4-hydroxy-N-(1"-") set that isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-Teres chexanamide hydrochloride salt all bisas cas incipulos 15 to The compound of Example 53(a) (12 mg/20.014 mmol) was stirred in methanol:water (9:1) with 1M HCla (2:eq) in ether overnight. The solvents were removed in vacuo to give the title compound (8 mg, 73%). NMR(CD3OD) (δ 7.35) (2H,s), 7.31 $t_{\rm in} = 0.85$ (15H, m), 5.00 (2H, s), 44.59 (1H, 0d), 4.15 (1H, 0d, ## 0 20 5 rotamers), 4.65+ 4.48(1H, t, rotamers), 4.81(計 4.38)(2H, dd), 3.80 (2H,d), 3.59 (1H, m), 3.40 (1H, d), 2.85-2.48 (5H, m), 2.00 (1H, m), 1.60 (1H, m), 1.55 (1H, m), 1.31 (3h, s), 1.29

There 25 the man in fact the second in the set Example 54 11 a good strongered the

(3H,s), 0.91 (3H, d), 0.60 (3H, d),

Preparation of (2R.4S.5S.1'S)-5-((1.1-dimethyl-2-08).

glycyloxy)ethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide

dihydrochloride salt

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- a) (2R, 4S, 5S, 1'S) -5-(1, 1-dimethyl-2-ii. in describing the glycyloxyethoxycarbonyl) amino-4-(t-butyldimethylsilyl) oxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-
- The compound of Example 53(a) (58)mg, 4.0678mmol) was stirred in methanol with 10% Pd/C (50 mg) under 1 atm hydrogen overnight. The reaction mixture was filtered

through C lite® and the solvents were removed in vacuo to yield the title compound (48 mg, 98%). NMR(CD3OD) & 7.32-7.02 (10H, m), 6.99 (2H, s), 4.68 (1H, d), 4.40-4.28 (2H, dd), 3.81 (2H, d), 3.80-3.67 (2H, m), 2.90-2.49 (5H, m), 2.15 (1H, m), 5 1.97 (1H, m), 6.48 (1H, m), 1.40 (3H, s), 1.39 (3H,s), 1.15 (3H, d), 0.95 (9H, s), 0.70 (3H, d), 0.11 (6H, d).

b) (2R, 4S, 5S, 1'S) -5-((1, 1-dimethyl-2-glycyloxy) ethoxy-carbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide dihydrochloride salt

The compound of Example 54(a) (43.5 mg, 0.060 mmol) was stirred in methanol:water (9:1) with 1M HCl in ether (0:12 mL, 2 eq) for 2 d. The solvents were removed in vacuo and 15 the product was trituated with ether:methanol (20:1) to yield the title compound (40 mg, 98%). NMR(CD3OD) & 7.35 (2H, s), 7.30-6.92 (10H, m), 4.60 (1H, d), 4.25 (2H, dd), 3.75 (2H, d), 3.59 (1H, m), 3.49 (1H, m), 2.90-2.51 (6H, m), 2.10 (1H, m), 1.65 (1H, m), 1.54 (1H, m), 1.30 (6H, s), 0.90 (3H, d), 2.20 0.60 (3H, d).

· (# JAC 1 - D. C. V. V. VAL) Take Vin Example 55

08.8 (Preparation of (2R.4S.5S.1'S)-5-((1.1-dimethyl-2-

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- hydroxy)ethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-(4-isopropylcarbonylimidazol-2-yl))methyl-6-phenyl-2phenylmethyl-hexanamide_dihydrochloride_salt
- a) (2R, 4S, 5S, 1'S)-5-amino-4-t-butyldimethylsiloxy-N-[1'-30 isopropyl-1'-(4-isopropylcarbonyl-imidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide
- Using the procedure of Example 13(a), except substituting the compound of Example 28(d), the title compound was prepared.
- hydroxy) ethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-(4-

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Following the procedures of Example 38(b)-38(c), except

isopropylcarbonylimidazol-2-yl))methyl-6-phenyl-2-sphenylmethyl-hexanamide dihydrochloride salt

substituting the compound of Example 55(a) for (2R, 4S, 5S, 1'S) -5-amino-4-t-butyldimethylsiloxy-N-('- isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide, the title compound was prepared. NMR (CDCl3) δ 7.49 (1H, s), 7.13 (5H, m), 6.84 (5H, m), 5.53 (1H, d), 4.47 (1H, d), 3.79 (1H, m), 3.60 (1H, m), 3.44 (2H, m), 3.16 (1H, m), 2.81-2.50 (5H, m), 1.92 (1H, m), 1.62 (2H, m), 1.18 (14H,

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Preparation of (2R.4S.5S.1'S)-5-((1S)-1-methyl-2-hydroxyethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethylhexanamide

m), 0.72 (3H, d), 0.58 (3H, d); MS m/e 621.4 [M+H]+.

Using the procedure of Example 41, except substituting
20 2(S)-t-butyldimethylsiloxy-1-methylethanol in 41(a) (prepared from 2(S)-1,2-propanediol), the title compound was prepared.

NMR(CD3OD) δ 7.38-6.90 (10H, m), 6.83 (2H, s), 4.58 (2H, m),
3.61 (1H, m), 3.34 (3H, m), 2.82-2.44 (5H, m), 2.00 (1H, m),
1.66 (1H, m), 1.52 (1H, m), 1.08 (3H, d), 0.85 (3H, d), 0.60
25 (3H, d).

Example 57

- Preparation of (2R.4S.5S.1'S)-5-((1R)-1-methyl-2- ()

30 hydroxyethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'imidazol-2-yl)methyl-6-phenyl-2-phenylmethylhexanamide

Using the procedure of Example 41, except substituting 2(R)-t-butyldimethylsiloxy-1-methylethanol in 41(a), the title compound was prepared. NMR(CD3OD) δ 7.39-6.88 (10H,

35 m), 6.82 (2H, s), 4.56 (2H, m), 3.60 (1H, m), 3.36 (3H, m), 2.81-2.45 (5H, m), 1.99 (1H, m), 1.65 (1H, m), 1.51 (1H, m), 1.03 (3H, d), 0.84 (3H, d), 0.60 (3H, d).

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Preparation of (2R.4S.5S.1'S) -5-((1-acetyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-

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phenylmethylhexanamide management and the state of the st

The title compound was prepared by the procedure of Example 13(a)-(c), except substituting acetic anhydride in place of isopropyl chloroformate. NMR(CD3OD) & 7.21-6.90 (10H, m), 6.81 (2H, s), 4.58 (1H, d), 3.98 (1H, m), 3.51 (1H,

10 m), 2.85-2.49 (5H, m), 1.99 (1H, m), 1.68 (3H, s), 1.61 (3H, s), 1.50 (1H, m), 20.80 (3H, sd), 0.60 (3H, sd).

A(0) A(0) B(0) A(0) A(0) B(0) B(0) B(0) B(0) B(0) B(0) B(0)

hydroxy-N-(1'-isopropyl-1'imidazol-2-yl)methyl-6-phenyl-2-(4-benzyloxyphenylmethyl) hexanamide

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- a) (3R,5S,1'S)-(1'-t-butoxycarbonylamino-2'-phenyl)ethyl-3-
- (4-benzyloxy) benzyl bromide, the title compound was prepared (284 mg, 27%). NMR(CDCl3) & 7.48-6.72 (14H, m), 4.94 (2H,
- (p. JECb) E(2R, 4S, 5S)=5-(t-butoxycarbonyl) amino-4-t-butyldimethyl-(c. JECb) Siloxy-6-phenyl-2+(4-benzyloxyphenylmethyl) hexanoic acid Following the procedure of Evans et al., Ed. Org. Chem.
 - 50, 4615 (1985), except substituting the compound of Example 59(a) for benzyl bromide, the title compound was prepared. NMR(CDCl₃) δ 7.42-6.76 (14H, m), 4.99 (2H, s), 4.69 (1H, d), 3.91 (1H, q), 3.66 (1H, m), 2.98-2.36 (5H, m), 1.85 (1H, m), 1.52 (1H, m), 1.30 (9H, s), 0.88 (9H, s), 0.04 (6H, m).
 - c) (2R, 4S; 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-(4-benzyloxyphenylmethyl) hexanamide

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Following the procedure of Example 12(c), except using
           (b), the title compound was prepared (284 mg, 92%).
The command NMR (CDCl3) δ 7.42-6.74 ((16H; m), 5.041 (2H; s), 54.99 (1H, d),
          4.77 (1H, d), 4.51 (1H, dd), 3.93 (1H, q), 3.69 (1H, m),
          2.80-2.39 (5H, m), 1.81 (1H, m), 1.62 (1H, m), 1.33 (9H, s),
    20 0.92 (9H, s), 0.75 (6H, dd), 0.07 (6H, d) 1 05%
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d) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(4-0)

(B) 10 benzyloxyphenylmethyl) hexanamide (B) 84.5-38.2 (m 03 Following the procedure of 12(d), except using (c), the title compound was prepared (100 mg, 94%). NMR(CD3OD) δ 7.41-7.09 (10H, m), 6.85 (2H, d), 6.79 (2H, s), 6.58 (2H, d), 5.41 (1H, d), 4.90 (2H, s), 4.47 (1H, d), 3.62 (1H, q), 3.48 15 (1H, d), 2.79-2.48 (6H, m), 2.02 (1H, m), 1.62 (2H, m), 1.33 -A) Stay (9H, s), 0.74 (3H, d), 0.61 (3H, d) a E-11 - East mined

Example 60

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- Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4-DELEG hydroxy-N-(1'-isopropyl-1'imidazol-2-yl)methyl-6-phenyl-2-(4because a hydroxyphenylmethyl) hexanamide (Tyanac (Yanac hydroxyphenylmethyl) (20% mg 25%), h man (cocks) & c. 4. -t. 72 (cos. -t., 4. St. (cos.)
- Following the procedure of Example 4(b) except using the compound of 59(d), the title compound was prepared (56 25 mg, 86%). NMR(CD3OD) δ 7.18 (5H, m), 6.84 (2H, s), 6.73 (2H, raysis ad), 6.44 (2H, d), 5.32 (1H, d), 4.45 (1H, d), 3.61 ((1H, q), 5 3.42 (1H, m), 2.80-2.42 (5H, m), 2.04 (1H/cm), 1.61 (2H, m),

30, 4 ins (1984), owners from the state of the state of 108 and there is to the larger than query of the ad Example 61 against woll (area Mest (C 1013) 8 7. . . . 15.76

Preparation of (2R:4S:5S)-5-(t-butoxycarbonyl)amino-4hydroxy-2-phenylmethyl-6-phenyl-N-[1.'-cyclopropyl-1'imidazol-2-vllmethyl-hexanamide

> a) α -(t-butoxycarbonyl)-amino- α -cyclopropylacetonitrile

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To a solution of cyclopropylmethanol (10.2 g, 141 mmol) five the combined chloride (250 mL) sodium acetate (1 g) and 20 g of Celite® were added. Pyridinium chlorochromate (30 g, 140 mmol) was added in small portions over a period of 30 m.

Ship San After 1 h the reaction mixture was diluted with ether and washed with ether. The combined organic extracts (1 L) were concentrated in vacuo at 15-18°C to yield formyl cyclopropane.

The crude aldehyde was dissolved in water (50 mL), and ammonium chloride (6.51 g), potassium cyanide (7.16 g) and aqueous ammonium hydroxide (100 mL, 28% w/w). The reaction mixture was stirred at room temperature overnight, extracted with ethyl acetate, and the combined organic extracts were dried over MgSO4. Filtration and evaporation of the solvent in vacuo yielded α-amino-α-cyclopropyl acetonitrile as an oil.

To a solution of the crude aminonitrile (2 g) in THF (20 mL) di-tert-butyldicarbonate (1.53 g, 7 mmol) was added. The reaction was stirred overnight. Removal of the solvent in 20 vacuo followed by flash chromatography (silica, 1:8 ethyl acetate:hexane) yielded the title compound (2.8 g). 1H NMR (CDCl₃, 200 MHz) δ 5.0 (bs, 1H), 4.4 (bs, 1H), 1.4 (s, 9H), 1.2 (m, 1H), 0.7 (m, 2H), 0.5 (m, 2H).

(c) 25 (c) b) α-(t-butoxycarbonyl)-amino-α-cyclopropylacetaldehyde

To a solution of the compound of Example 61(a) (1 g, 5.1 mmol) in THF (20 mL), diisobutylaluminium hydride (10.5 mL, 10.5 mmol, 1M in THF) was added at -78°C, over 5 min. The reaction mixture was allowed to warm to 0°C over a period of 30 2 h, and stirred at 0°C for an additional 1 h. The reaction mixture was quenched with MeOH (2 mL), and saturated potassium sodium tartrate solution (100 mL) was added.

Extraction with ether, drying over MgSO4 and removal of solvents in vacuo yielded an oil. Flash chromatography 35 (silica, 1:10 ethyl acetate:hexane) gave the title compound as a colorless solid (225 mg). NMR(CDCl₃, 400 MHz) & 9.45 (bs, 1H), 4.95 (bs, 1H), 3.5 (bs, 1H), 1.3 (s, 9H), 0.7 (m, 1H), 0.3-0.6 (m, 4H).

c) 1-(t-butoxycarbonyl)amino-1-(imidazol-2-yl)-1-cyclopropyl-methane

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A mixture of the compound of Example 61(b) (178 mg, 0.89 mmol), glyoxal (150 mL, 1 mmol, 40% aq), ammonium hydroxide (5 mL, 28% aq) and MeOH (5mL) was stirred at room temperature for 10 h. The solvents were removed in vacuo and the residue was titurated with ether to yield a brown solid (53 mg). The solid was passed through Florisil® and eluted with 5% MeOH/methylene chloride. Removal of the solvent in vacuo followed by trituration provided the title compound as a colorless solid (19 mg). MS(CI/NH3) m/e 238.3 [M+H]+· 1H NMR(CD3OD, 200 MHz) & 6.9 (s, 2H), 4.1 (bd, 1H), 1.4 (s, 9H), 1.3 (m, 1H), 0.6 (m, 2H), 0.4 (m, 2H)

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1:

:255

d) 1-amino-1-(imidazol-2-yl)-1-cyclopropyl-methene, in trifluoroacetate and process and the control of the cont

The compound of Example 61(c) 1 (15 mg) awas dissolved in 1 will be mL of TFA and stirred at room temperature for 20 min.

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Burney of T.O. (C.T. on) C.R. (1998)

- 20 Solvents removed in vacuo to give the title compound as a semisolid residue.

 ¹H NMR (CD₃OD, 200 MHz) δ7.1 (s, 2H), 3.8 (d, 1H, J=7 Hz), 1.5 (m, 1H), 0.5-0.8 (m, 4H).
- e) (2R, 4S, 5S)-5-(t-butoxycarbonyl)amino-4-(t-butyldimethyl)
 25 siloxy-2-phenylmethyl-6-phenyl-N-[1'-cyclopropyl-1'-imidazol
 2-yl]methyl-hexanamide

The compound of Example 61(d) was dissolved in DMF (2 mL) and NMM (26 mg, 0.25 mmol) was added and the solution was stirred at 0°C for 30 min. (2R,4S,5S)-2-phenylmethyl-4-(t-

butyldimethyl)siloxy-5-(t-butoxycarbonyl)amino-6-phenyl hexanoic acid (38 mg, 0.07 mmol) and BOP reagent (30 mg, 0.07 mmol) were added and the reaction was stirred at room temperature for 24 h. The reaction was diluted with ethyl acetate (100 mL), washed with aqueous sodium bicarbonate and dried over anhydrous potassium carbonate? Removal of solvents in vacuo, followed by flash chromatography (silica, 5% methanol/methylene chloride) yielded the title comp und as

a mixture of diastereomers (25 mg)(#4 ...) 6.0-8.0 (86

1986 Burgary end of the min f) % (2R, 4S, 5S) -5- (t-butoxycarbonyl) amino-4-hydroxy-2-The phenylmethyl-6-phenyl-N-[1'-cyclopropyl-1'-imidazol-2-O. g yl]methyl-hexanamide

70.

(Till 50) The compound of Example 61(c) was dissolved in THF (2 ml) and tetrabutyl ammonium fluoride (200ml, 1M in THF) was added. The reaction was stirred at room temperature grand overnight and methylene chloride (100 mL) and water (10 mL) also required added. The organic layer was dried over potassium carbonate, and the solvent was removed in vacuo to give an

oil. Flash chromatography (silica, 5% methanol/methylene chloride) gave a colorless solid which was a 1:1 diastereomeric mixture of the title compound. milliform II is here to be made to the

15 James of Linder Comments of La DExample 62

rapid to NOTE 18, Parties

Preparation of (2R.4S.5S.1'R)-5-(t-butoxycarbonyl)amino-4hydroxy-2-phenylmethyl-6-phenyl-N-[1'-cyclopropyl-1'rivgoscos imidazol-2-yllmethyl-hexanamide: and las is.

A DESCRIPTION OF A MILE

- (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-2phenylmethyl-6-phenyl-N-[1'-cyclopropyl-1'-imidazol-2vllmethyl-hexanamide, 1,2%, 1 and a system of the
- paragrame of the lateral analogates with outgoing a great of the last organism. CAME is in a) Purification of the 125 mg of the compound of Example 61(e) by flash chromatography (silica, 3% methylene chloride/methanol), yielded 48 mg of isomer 1, 15 mg of home has isomer 2 and 20 mg of combined fractions. 1H NMR for isomer as rot 5.1H), 4.85 (d, 1H), (4.15 (dd, 1H), (3.75(q, 1H), 3.6(m, 1H), 30 Hat. 2.9 (dd, (1H) /2.2.7. (d, (2H), 2.6 (dd, (1H), (2.3 (m, 1H), 2.0 (m, and to 1H), 1.6 (m, 1H), 1.4 (m, 1H), 1.35 (s, 9H), 0.95 (s, 9H), $m_{0} \approx 10.7 \text{ (m, s) 1H), } 0.4 \text{ (m, (1H), 0.25 (m, s) 1H), 0.1 (m, s) 1H), 0.2 (s,$ 3H), 0.1 (s, 3H), 1H NMR for isomer 2 (CDCl₃, 400 MHz) 87.1svin of 7.4% (m, 10H) $\approx 6.8\%$ (s, 2H) ≈ 6.26 (d, 1H), 4.6% (d, 1H), 4.0% (m, 2H), 2.5-3.0 (m, 4H), 1.8 (m, 1H), 1.7 (m, 1H), 1.5 (m, 1H), 1.4 (s, 9H), 1.0 (s, 9H), 0.7 (m, 2H), 0.2 (m, 2H), 0.1 (2 overlapping singlets, 6H).

11.12 1975 J.

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b) Following the procedure of Example 61(f), except "substituting the compounds of Example 62(a) vielded the title compounds. ¹H NMR for isomer 1 ((CD₃OD, 400 MHz) % δ 7.1-7.3 (m, 10H), 6.95 (s, 2H), 4.25 (d, 1H), 3.5-3.7 (m, 2H), 2.5-3.0 (m, 5H), 1.7 (m, 2H), 1.4 (s, 9H), 1.1 (m, 1H), 0.6 (m, 1H), 0.25-0.4 (m, 2H), 0.05 (m, 1H); MS (ESMS) m/e 533.2 [M+H]+; 1H NMR for isomer 2 (CD₃OD) δ 7.1-7.4 (m; 10H), 6.85 (s, 2H), 4.25 (d, 1H), 3.5-3.7 (m, 2H), 2.5-2.9 (m, 5H), 1.5-1.8 (m, 2H), 1.4 (s, 9H), 1.1 (m, 1H), 0:2-0.6 (m, 4H); MS(ESMS) m/e 10 "533.4 [M+H]+. There I have be order took took had headingth ap-

Common of trend post specific markets er last Example 63 a swip (obliveled-

o - There is worth with a bismoore duck.

Preparation of (2R.4S.5S.1'S)-5-((isopropylthiol)carbonyl)amino-4-hvdroxv-2-phenvlmethvl-6-phenvl-N-[1-isopropvl-1'imidazol-2-vllmethvl-hexanamide

a) 5-((isopropylthiol)carbonyl)amino-4-(t-Schessed butyldimethylsiloxy) -2-phenylmethyl-6-phenyl-N-[1 -isopropyl-1'-(1-(isopropylthiol) carbonyl-imidazol-2vl)]methylhexanamide

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To a solution of (2R, 4S, 5S, 1'S) -5-amino-4-tbutyldimethylsiloxy-2-phenylmethyl-6-phenyl-N-[1'-isopropyl-1'-imidazol-2-yl]methyl-hexanamide (81 mg, 148 mmol) and DMAP (37 mg, 303 mmol) in dichloromethane (8 mL), yd (a) 18 isopropylthiolchloroformate (42 mg/ .303 mmol) in (25) dichloromethane (1:mL) was added. The solution was stirred for 20 h and an additional equivalent of the chloroformate and DMAP were added. The reaction mixture was stirred for an additional 20 h, diluted with dichloromethane, and washed with saturated sodium bicarbonate. The organic extract was dried over magnesium sulfate, filtered and evaporated to an oil. The oil was dissolved in chloroform and purified by flash chromatography (silica, 1% methanol/chloroform) to give 35 the title compound as an oil (79.5 mg) (10.6 % % , GRY

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(grandous b) 4 (2R, 4s, 5s, 1's) -5- ((isopropylthiol) carbonyl) amino-4hydroxy-2-phenylmethyl-6-phenyl-N-[1-isopropyl-1'-imidazol-2-. (Furn yl]methyl-hexanamide anormas of Furn product

To a solution of the compound of Example 63(a) (79 mg, min 5 (105 mmol) in methanol (8 mL), 10% hydrochloric acid (3 mL) was added. The reaction mixture was stirred overnight at 25°C. The methanol was evaporated in vacuo, and the residue file that hwas diluted with water the solution was neutralized with 5% Description and a solid precipitated. 10 solid, was filtered, washed with water, and triturated with up 808.9) ether. co The solid was dried at high vacuum to yield the title compound (27 mg, 48%). NMR(CDCl3, 250 MHz) δ 6.9-7.3 (m, 10H), 6.85 (s, 2H), 6.20 (d, 1H), 4.42 (d, 1H), 4.22 (m, 1H), -£4.0%(m, 1H),£3.55%(m, 3H), 2.5-3.0 (m, 6H), 1.65 (t, 2H), - 1115 - 1.27 (m, 7H) / 1.71 (d-ofed, 6H); MS (FAB) m/e 537 [M+H]+; TLC Rf 0.30 (silica, 4% methanol/chloroform).

Example 64

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Lin baha la

ann LVI) - Well signess to demonstrate with the noise the K Ex20 Preparation of (2R.4S.5S.1'S) 5-(1-hydroxymethyl- 10 (Ba (E) orcyclopentyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexamide enabled entires of washed with the negligible readonance

with dentification and successful to be typicated by the property of the

edf (t-butyldimethysiloxy) methyl-cyclopentanol 25 A Fighton a solution of 1-hydroxymethyl-1-cyclopentanol (4.07 served g, 0.035 mole) in dichloromethane (30 mL) t-butyldimethylsilyl chloride (5.28 g, 0.035 mol) in dichloromethane (30 mL) was added. Triethylamine (5.37 mL, 0.0385 mol) and DMAP (0.171;g, 0.0014 mol) were added and the solution was stirred 30 overnight at 25°C. The solution was diluted with. dichloromethane (30 mL) and washed with water and saturated 831 (ammonium chloride solution. The organic solution was dried bear over sodium sulfate, filtered and the solvent removed at becoreduced pressure. The product was purified by flash 1 16 35 chromatography (silica, 19:1) hexane:ethyl_acetate) to yield the title compound as a colorl ss oil (6.95 g, 86%). been 1.7-7. He is contained the course seach wi

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b) 1-(t-butyldimethylsiloxy)methyl-cyclopentyl 4-nitrophenyl carbonate

A solution of the compound of 64(a) (1.15 g, 5 mmol),

DMAP (0.611 g, 5 mmol) and bis (4-nitrophenyl) carbonate (1.52

5 g, 5 mmol) in dichloromethane (16 mL) was stirred overnight

at 25°C. The reaction mixture was diluted with

dichloromethane and washed with 5% sodium carbonate. The

solvent was removed at reduced pressure and the residual oil

was triturated with hexane:ethyl acetate (3:2) and filtered.

10 The product was purified by flash chromatography (silica,

19:1 hexane:ethyl acetate) to give a colorless oil (0.599 g,

30%).

c) (2R, 4S, 5S, 1'5)-5-[1-(t-butyldimethylsiloxy) methylcyclopentyloxycarbonyl] amino-4-t-butyldimethylsiloxy-N-[1'isopropyl-1'-(t-butyldimethylsiloxy) methylcyclopentyloxy) imidazol-2-yl]-6-phenyl-2-phenylmethylhexanamide

A solution of the compound of Example 13(a) (173 mg, 0.316 mmol), DMAP (81 mg, 0.663 mmol) and the compound of Example 64(b) (262 mg, 0.663 mmol) in dichloromethane (10 mL) was stirred for 48 h at 25°C. The organic solution was diluted with dichloromethane, washed with 5% sodium carbonate solution and the solvent removed at reduced pressure. The product was purified by flash chromatography (silica, 4:1hexane:ethyl acetate) to yield the title compound as an oil (200 mg, 60%).

d) (2R, 4S, 5S, 1'S) 5-(1-hydroxymethyl-cyclopentyloxy30 carbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2yl) methyl-6-phenyl-2-phenylmethyl-hexamide ***

A solution of the silated derivative (200 mg, 0.188 mmol) in methanol (7 mL) and 3N HCl (2.5 mL) was stirred overnight at 25°C. The methanol was removed at reduced pressure and the solution was diluted with water (15 mL) and extracted with ether (25 mL). The aqueous solution was neutralized with 5% sodium carbonate solution to pH 7-7.5 and the product precipitated as a solid. The solid was filtered,

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washed with wat r and dried in vacuo to yield the title compound (51 mg, 47%). NMR (CD3OD, 400 MHz) & 7.0-7.3 (m, 10H), 6.87 (s, 2H), 4.62 (d, 1H), 3.70 (m, 3H), 3.55 (d, 1H), 2.5-2.9 (m, 5H), 2.05 (m, 1H), 1.5-2.0 (br, 10H), 0.88 (d, 5) 3H), 0.70 (d, 3H); TLC R_f (0.50 (silica, 8% methanol/chloroform).

Sorgram of the transfer distribution of Example 65.

Preparation of (2R.4S.5S.1'S)-5-[3-(R)-(1H-imidazol-2-yl)-3
hydroxy-4-methylpentylamidol-4-hydroxy-N-(1'-isopropyl-1'
imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide: and

(2R.4S.5S.1'S)-5-[3-(S)-(1H-imidazol-2-yl)-3-hydroxy-4
methylpentylamidol-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2
yl)methyl-6-phenyl-2-phenylmethyl-hexanamide:

tionion of all retransports on the law of the one of the configuration

(32年) a) 1-(1-benzyloxymethylimidazol-2-yl)-2-methyl-1-propanol Compared according to the procedure of Ngochindo, R., J. Chem. Res. (S) 58 (1990)) thest 2000 (3.76 g, 20 mmol), and THF (40 mL) at -40°C, was treated The dropwise with n-Buli (8.4 ml, 21 mmol, 2.5 m in hexane). The quadresulting solution was stirred at 1-40°C for 15 min, and i-Massachutyraldehydem (2.0 mL, 22 mmol) was added dropwise. The 78.3 reaction was stirred at -40°C for 1.5 h, 0°C for 1 h, warmed 25 to 23°C, poured into H2O, and extracted with EtOAc. The combined extracts were washed with brine, dried (Na2SO4) and (a) SECTION Concentrated in vacuo. Trituration of the residue with physical Et20/hexane gave a white solid which was dried in vacuo overnight to afford of the title compound (3.57 g, 69%). 30 NMR (CDCl₃, 400 MHz) δ 7.28 (m, 5H), 6.97 (s, 1H), 6.92 (s, Jan. 1H), 5.23 (d, (1H, J=12 Hz), 5.42 (d, 1H, J=12 Hz), 4.48 (s, 2H), 4.44 (d, 1H, J=9 Hz), 2.21 (m, 1H), 1.02 (d, 3H, J=7traw Hz) , a 0.183: (d, g 3H, J=7, Hz) . Let arvis 1 of any or a graph

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added and stirring was continued for an additional 2 d. Filtration through Celite®, concentration and flash chromatography (silica, 0-1% CH₃OH/CH₂Cl₂) afforded the title compound (0.773 g, 77%). ¹H NMR(CDCl₃, 400 MHz)-7.28 (m, 6H), 7.18 (s, 1H), 5.85 (s, 2H), 4.52 (s, 2H), 3.94 (m, 1H), 1.21 (d, 2H, J=5 Hz).

c) t-butyl 3-(1-benzyloxymethylimidazol-2-yl)-3-hydroxy-4-methyl-pentanoate

Diisopropylamine (83 µL, 0.59 mmol) and THF (1.5 mL) were cooled to -40°C and n-BuLic(188 µL) 0:47 mmol, 2.5M in hexane) was added. The reaction mixture was warmed to -10°C and stirred for 15 m. recooled to -70°C and t-butyl acetate 13 μL, 0.47 mmol) was added. The reaction was stirred for 5 m, and HMPA (254 µL, 1.41 mmol) was added The reaction was stirred at -70°C for 5 m and 1-(benzyloxymethylimidazol-2y1)-2-methyl-propan-1-one (100 mg, 0:39 mmol) (in THF (1.5 mL) was added dropwise. The mixture was stirred at -70°C for 30 m, -40°C for 30 m, -10°C for 30 m, warmed to 23°C; poured 20 into 10% aqueous K2CO3 and extracted with EtOAc. The combined organic extracts were washed with brine, dried (K2CO3), concentrated and flash chromatographed (silica gel, step gradient, 0-20% EtOAc/hexanes) to afford the title compound beauty (131 mg, 90%). 31 NMR (CDCl3, 3400 MHz) δ 7325 (m, 35H), 6.96 25 (s, 1H), 6.91 (s, 1H), 5.69 (d, 1H, J=10 Hz), 5.65 (d, 1H, J=10 Hz), 4.53 (d, 1H, J=11 Hz), 4.48 (d, 1H, J=11 Hz), 3.23 (d. 1H. J=6 Hz), 2.57 (d, 1H, J=6 Hz), 2.14 (m, 1H), 1.39 (s, 9H); 0.97 (d, 3H, J=7 Hz); 0.75 (d, 3H, BJ=7 Hz); MS(ES) m/e salara just in book so of infolioresmo-375 [M+H]+. THER (CD CLOSE FOR MORE & PLUE BY THE STATE OF THE STATE

d) 3-(1-benzyloxymethylimidazol-2-yl)-3-hydroxy-4-methyl pentanoic acid triflouroacetate

The compound of Example: 65(c) (93 mg, 0.24 mmol) was dissolved in TFA (1 mL) and stirred for 20 m. The TFA was removed in vacuo to give the title compound (102 mg, 100%).

1H NMR(CDCl₃, 400 MHz) 7.30 (m, 7H); 6.06 (d, 1 H, J=9 Hz),

5.74 (d, 1H, J=1 Hz), 4.67 (d, 1H, J=9 Hz), 4.61 (d, 1H, J=9 Hz), 3.62 (d, 1H, J=12 Hz), 2.93 (d, 1H, J=12 Hz), 2.93 (d, 1H, J=12 Hz), 2.04 (m,

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To but 1H), 0.92 (d, 3H, J=12 Hz), 0.88 (d, 3H, J=12 Hz); MS(ES) m/e
s byolte .319 [M+H] taby i swellens.
                                                                                     TWO ENDS
    estation in a large ment of the large of the second
  . ground and e) (2R,4S,5S,1'S) = 5-[3-(RS)-(1-benzyloxymethylimidazol-2-yl)-
      68:5 ps 3-hydroxy-4-methylpentanoyl]amino-4-t-butyldimethylsilyloxy-
                 N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
      - phenylmethyl-hexanamide
 entry compound of Example 65 (d) (1.0 eq)
                (2R, 4S, 5S, 1'S) -5-amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-
 138.010 .. 2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide (1.1 eq), BOP
    (filt (e reagent) (1.1 eq) and triethylamine (4 eq) were reacted
  (History) according to the procedure of Example 1(c). The product was
 ( ) purified by flash chromatography to afford the title compound
               (57%) (silica, step gradient, 0-4% CH3OH/CH2Cl2). 1H
    15 NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.36-6.76 (m, 19H), 5.65 (m, 2H), 4.66
    (m, 1/2H), 24.51, (m, 2H), 4.39 (m, 1/2H), 4.30 (m, 1/2H), 4.02
                 (m,~1/2H),63.685 (m,61H), 3.28 (m,81H), 2.90-2.35 (m, 6H),
18. 2.13 (m, 1H), 1.76 (m, 1/2H), 1.68 (m, 1/2H), 1.40 (m, 1/2H),
  (成於 5 至1.00-0.70 (m, 21H), 0.10-0.00 (m, 6H); MS(ES) m/e 849 [M+H]+.
  A (Hi20,m) - EE.S A GIR (m) - Days - C. C., on the control of the 
(田公正 145) (2R, 4S, 5S, 11S) =5-[3-(RS)-(1-benzyloxymethylimidazol-2-yl)-
              3-hydroxy-4-methylpentanoyl]amino-4-hydroxy-N-(1'-isopropyl-
 1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide
                         The compound of Example 65(e) (100 mg, 0.12 mmol) was
               desilylated by the procedure of 47(c) to cleanly afford the
military title compound (78 mg, 89%). 1H NMR (CDC13, 400 MHz) 8 7.40-
     managa6.80.5(m, 19H), 5.75 (m, 2H), 4.97 (m, 1/2H), 4.78 (m, 1/2H),
    3.51 (m, 2H) 3.94 (m, 1/2H) 3.85 (m, 1/2H) , 3.51 (m, 1H),
               3.21 (m, 1H), 2.97-2.43 (m, 6H); 2.00 (m, 1H), 1.60 (m, 1H),
     30 -1.43 (m, 1H); 0.97-0.49 (m, 12H); MS(ES) m/e 735 [M+H]+:
                                 m(%) if a life going and if $100 country of the
-Ivides (1g): (2R, 4S, 5S, 1'S) -5-(3(R)-(imidazol-2-yl)-3-hydroxy-4-
               methylpentanoyl]amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-
   pakas (2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide; and
-1-4350 kg(2R, 4S, 5S, 1'S) -5-[3-(S)-(imidazol-2-yl)-3-hydroxy-4-
  - Lydde methylpentanoyl]amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-
   ed.: (2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide
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Using the procedure of Example 47(d), the compound of Example 65(f) (72 mg, 0.98 mmol) was hydrogenated to afford a · diastereomeric mixture of the title compounds. The mixture was purified by flash chromatography (silica, step gradient, 0-8% CH3OH/CH2Cl2) to afford tail fractions containing the pure diastereomers (35 mg total, 58%) (1900 decimination)

Isomer 1, last eluting, (2R, 4S, 5S, 1'S) -5-[3-(R)-(1H-Imidazol-2-yl)-3-hydroxy-4-methylpentylamido]-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-10 phenylmethyl-hexanamide. ¹H NMR (CDCl₃, 400 MHz) δ 7.35-6.82 (m, 10H), 6.93 (s, 1H), 6.84 (s, 1H), 4.42 (d, 1H, J=9 Hz),3.77 (m, 1H), 3.40 (m, 1H), 3.00-2.40 (m, 5H), 2.14 (m, 1H), 1.99 (m, 1H), 1.56 (m, 1H), 1.47 (m, 1H), 0.93-0.64 (m, 12H); MS(ES) m/e 615 [M+H]+1 and MF mg (stry emiliar) (NF)

Isomer 2, first eluting, (2R, 4S, 5S, 1'S) -5-[3(S)-(1H-Imidazol-2-yl)-3-hydroxy-4-methylpentylamidol-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide. 1H NMR (CDCl₃, 400 MHz) δ.7.35-6.81 (m, 10H), (6.83 (s, 1H), 6.81 (s, 1H), 4.46 (d, 61 H, J=9 Hz),3.93 (m, 1H), 3.40 (m, 1H), 3.00-2.40 (m, 5H), 2.13 (m, 1H), The way MS (ES) m/e 615 [M+H] +. Or to admit the war to war the state of the state

Example 66

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Preparation of (2R.4S.5S.1'S) -5~[(4-methoxyphenoxy) carbonyl]amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6phenyl-2-phenylmethyl-hexanamide in 1818 the late the

3.12 (0) 31 (0) 41 (0) 20, 24, 24, 3 (0) 25.6

30 a) (2R, 4S, 5S, 1'S) - 5 - [(4-methoxyphenoxy) carbony1] amino-4-tbutyldimethylsiloxy-N-[1'-isopropyl-1'-(N'methoxycarbonyl)imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-15 1 hexanamide water was a first the second of the second o

Following the procedure of Example 13(b) except using p-methoxyphenyl chloroformate and (2R, 4S, 5S, 1'S) -5-amino-4-tbutyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide (114 mg, 0.21 mmol), the title compound was prepared (63%). NMR(CDC1₃), δ 7.44-6.76

** Tyr / Stage (m, 520H), 15.66m(m, 51H) か 5.18 (d, 1H), 3.4.40 (m, 1H), 3.83 +1 (s,3H), ± 34769 (m, ± 1 H), $\pm 3.73\%$ (s, ± 3 H), $\pm 2.96-2.50\%$ (m, ± 5 H), 2.05 (m, 5H), 1.60 (m, 1H), 0.94 (s, 9H), 0.79 (d, 3 H, J=7 Hz),TEND (1998) . 74 (S, 23H) 7 .0112 (S, 3H) .00.116 (S, 3H) ...

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and to be by typical seed by the

(1'-6' 11'b) (2R, 4S, 5S, 1'S)-5- (methoxycarbonyl) amino-4-hydroxy-N-(1'-((a) (()) isopropyl-1!-imidazol-2-yl)methyl-6-phenyl-2-phenylmethylthe state hexanamide says and the bare that I was a daily a draw

Following the procedure of Example 13(c), except using 10 withe compound of Example 66(a), The title compound was to prepared (32%). NMR (CDCl₃/CD₃OD), δ 7.36-6.84 (m, 16H), 4.49 (d, lH, J=9 Hz), 3.79 (s, 3H), 3.37 (m, 1H), 2.92-2.60 (m, 5H), 2.10-1.70 (m, 3H), 0.78 (d, 3H, J=7 Hz), 0.67 (d, 3H, (in _iJ=7 Hz); MS(ES) m/e 585 [M+H] +... Constitution of the second of the

W 15 5 30 30 0 (a v , 19.1)

い「Angelogia Act agas (aE) De <u>Example 67</u> · 」は、 いっし、(se

Preparation of (2R.4S.5S.1'S)-5-(t-butylaminocarbonyl)amino -4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-

20 phenylmethyl-hexanamide life white the control of the control o company to a control of the property of the property of the

(2R, 4S, 5S, 1'S) 5-(t-butylaminocarbonyl) amino-4-(tdeades butyldimethylsiloxy)-N-(1*-isopropyl-1*-imidazol-2-yl)methylleast 16-phenylmethyl-hexamide to the typese gail outside

1 (19825 1981) The compound of Example 13(a) 3 (0.13 g; 0.24 mmol) was dissolved in dichloromethane (3 mL) and t-butyl isocyanate PRUB (0.028 g, 0.29 mmol) was added. PAfter stirring at 30°C for * * NEWS 18th, the solvent@was removed under reduced pressure and the 08.% residue was chromatographed (silica, 2:3 ethylacetate:hexane) .30 to give the title compound as a white solid (0.12 g, 77%).

6.85 (2H, s), $(\delta.7.35-7.05)$ (12H, m), $(\delta.85)$ (2H, s), $(\delta.69)$ (1H, d, J=9 Hz), 4.60 (1H, t, J=8 Hz), 4.38 (1H, br), 4.24 (1H, q, J=8 Hz), 3.66 (1H, dd, J=4 Hz, 10 Hz), 2.95 (1H, dd, J=9Hz, 13Hz), 2.73(2H, m), 2.54 (1H, .dd, J=5 Hz, 13 Hz), 2.42 (1H,

and the bearing and the same

m), 1.82 (1H, m), 1.67 (1H, m), 1.22 (9H, s), 0.93 (9H, s), отмония 0.84% (3H, Md, MJ=7 Hz) , 0.79 (3H, d, J=7 Hz) , 0.08 (3H, s),

0.07%(3H, %s); MS(ES) m/e 648.4 [M+H]+. A and an action to the standard

: 35

ES.S. b) (2R, 4S, 5S, 1'S) -5-(t-butylaminocarbonyl) amino-4-hydroxy-N-

The compound of Example 67 (a) I (0.0338g, 0.05 mmol) was stirred in dry THF (0.25 mL) and tetrabutylammonium flouride (0.25 mL, 0.25 mmol) in THF was added; After 18 h at 50°C the reaction was cooled, diluted with ethyl acetate (25 mL), washed with water (5 mL), and dried (MgSO4); The combined organic extracts were filtered and concentrated in vacuo.

10 Chromatography (silica, 1:1 ethyl acetate: hexane) gave the title compound as a white solid (0.018 g, 66%) (2H, s), 4.58 (1H, d, J=9 Hz), 3.71 (1H, t, J=7 Hz), 3.52 (1H, d, J=9 Hz), 2.75 (4H, m), 2.53 (1H, dd, J=4 Hz, 12 Hz); 2.03 (1H, m), 1.76 (1H, m), 1.66 (1H, m), 1.22 (9H, s), 0.79 (3H, d, J=7 Hz), 0.67 (3H, d, J=7 Hz); MS(ES) m/e 534 [M+H]⁺

Example 68 in additions of

20 Preparation of (2R.4S.5S.1'S)-5-(methylaminocarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6phenylmethyl-hexanamide.

Following the procedure of Examples 67(a)-67(b), except substituting methyl isocyanate for t-butylisocyanate, the title compound was prepared (0.075 mg, 51%). Mp 253°C (dec); NMR (DMSOd⁶) 87.78 (1H, d, J=9 Hz), 7.80-6.96 (11H, m), 6.88 (2H, s), 5.78 (1H, d, J=5 Hz), 5.72 (1H, d, J=9 Hz), 4.84 (1H, d, J=4 Hz), 4.65 (1H, m), 3.68 (1H, q, J=7 Hz), 3.44 (1H, br), 2.74 (3H, m), 2.58 (1H, dd, J=7 Hz, 13 Hz), 2.50 (3H, s), 2.41 (1H, d, J=8 Hz), 1.92 (1H, m), 1.46 (2H, m), 0.72 (3H, d, J=7 Hz), 0.63 (3H, d, J=7 Hz); MS(ES) m/e 492 [M+H]⁺.

Example 69, (82) 85.3 (88801

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(a (115) St. 2 (m.

Preparation of (2R,4S,5S,1'S)-5-(phenylaminocarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6- ophenylmethyl-hexamide.

Following the procedure of Examples 67(a)-67(b), except substituting phenyl isocyanate for t-butylisocyonate, the title compound was prepared (87 mg, 79%). Mp 273°C (dec); NMR (DMSO-d6), 8.50 (1H; s), 7.81 (1H, d, J=9 Hz), 7.34-6.83(18H, m), 6.07 (1H, d, J=9 Hz), 4.99 (1H, d, J=4 Hz), 4.65 -Alexand(1H, at, J=8 Hz), 3.75 (1H, m), 3.52 (1H, br), 2.77 (3H, m), 2.66 (1H, m), 2.42 (1H, d, J=7 Hz), 1.89 (1H, m), 1.50 (2H, m), 0.68 (3H, d, J=7 Hz), 0.61 (3H, d, J=7 Hz); MS (DCI/NH3) му ру **м/е. 554.3**(в[М+Н] †. такк. Посторы вы выстройный дов

contracted and appearing the system in a selection of the contraction of the contraction of the contraction of $\hat{\theta}$ (as $\theta\in \mathcal{H}_{G}$) the \mathcal{H}_{G} (if $\theta\in \mathcal{H}_{G}$) θ (Example 70) and \mathcal{H}_{G}

1 10 g(2 182) 1821 (pr. 2021) 12. Her (1) g 2 1845 20 10 11 21 1 (2R, 4S, 5S, 1'S) -5-N-(propylaminocarbonyl) amino-4-hydroxy-N-SECTION (1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-

15 of hexamide to let 2 to the first (12) .8.0 (12) Following the procedure of Examples .67(a), except t she all substituting n-propyl isocyanate; for t-butylisocyanate, the title compound was prepared (0.048 g, 54%). Mp 247-9°C (dec); NMR (DMSO-d6) δ 7.75 (1H, d, J=8 Hz), 7.23-6.94 (11H, 20 m), 6.85 (2H, s), 5.87 (1H, t, J=5 Hz), 5.65 (1H, d, J=9 Hz), 4.82 (1H, d, J=4 Hz), 4.64 (1H, t, J=8 Hz), 3.66 (1H, m), 2.33.38 (1H, mbr), 2.87 (2H, q, J=6 Hz), 2.74 (3H, m), 2.56 (1H, dd, J=7 Hz, 13 Hz), 2.39 (1H, d, J=7 Hz), 1.91 (1H, m), 1.43 (2H, m), 1.28 (2H, q, J=7 Hz), 0.77 (3H, t, J=7 Hz), 0.71 25 (3H, d, J=7 Hz), 0.62 (3H, d, J=7 Hz); MS(CI) m/e 520.2 discourse to the second of the

sec 2 h. . There commend in a manch with the war pour bd into ase has the se estables a Example 71 49 6 4 as a made

not make classes only and soll a thing agreement of the Sv-30 ex Preparation of (2R, 4S, 5S, 1'S) -5-(n-propylaminothiono) amino-4hydroxy-N-(1'isopropyl-1'-imidazol-2-yl)methyl-6phenylmethyl-hexamide. Hoston where the introduction

\(\partial (\partial (a)) = 0^77 [Following the method of Example 67 (a) -67 (b) \(\text{c} \) except , (b) dusing n-propyl thioisocyanate, the title compound was 24.35 (prepared (0.012 g, 21%) . Mp, 195-7°C (dec); NMR (CD3OD) δ 《图1. 2017.32-6.86 (12H, 1m) ; 4.59 (1H, m), 3.64 (1H, br), 3.34 (2H, 904 (br), 2.79 (5H, m), 2.03 (1H, m), 1.73 (1H, m), 1.58 (3H, m), 0.92 (3H, t, J=7Hz), 0.83 (3H, d, J=7Hz), 0, 68 (3H, d, J=7 Hz); MS (CI) m/e 536.2 [M+H]+.1 y and wake a decomp

Example 72.8 (35-08/40) 2.74

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Preparation of (2R.4S.5S.1'S)-5-(isopropylaminocarbonyl)amino-4-hydroxy-N- (1'-isopropyl-1'-imidazol-2-yl)methyl-6phenylmethyl-hexamide (80 feet (80 kg) 8506 yes

Following the method of Example 67 (a) -67 (b) except substituting isopropyl isocyanate for t-butyl isocyanate, the title compound was prepared (0.034g, 46%). NMR(DMSO-d6) δ 7.78 (1H, d, J=8 Hz), 7.24-6.97 (11H, m), 6.85 (2H, s), 5.74 (1H, d, J=8 Hz), 5.57 (1H, d) J=9 Hz 4.83 (1H, d, J=4 Hz), 4.66 (1H, d, J=7 Hz), 3.62 (2H, m), 3.43 (1H, br), 2.73 (3H, 15 m), 2.57 (1H, dd, J=7 Hz, 13.5 Hz), 2.41 (1H, d, J=7 Hz), 3 | 1.91 | (1H, m), 1.45 | (2H, m), 0.95 | (3H, d) | (3H=6.5 | Hz), 0.93 | (3H, * d, J=6.5 Hz), 0.72 (3H, d, J=6.5 Hz); 0.63 (3H, d, J=6.5 Hz); in MS (CI) m/e:520.2 [M+H] +. Worder og asar handeren siddir

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3 Example 73 (3 (15) 28.0 (1)

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1000 (1011年) (10個7分級) (1800 (E19) (E2), 2

Preparation of (2R.4S.5S.1'S)-5-(aminocarbonyl) amino-4-69.2 hydroxy-N-(1'-isopropyl-1'-imidazol-2-v1)methyl-6- ab Description of the phenylmethyl-hexamide of t

25 The compound of Example 67(a) (0.050 g, 0.094 mmol) was dissolved in triflouroacetic acid (2 mL) and stirred at 50°C for 2 h. After cooling, the reaction mixture was poured into saturated sodium bicarbonate solution (50 mL) and was extracted into ethyl acetate (100 mL). The organic solution 30 was washed with brine, dried (MgSO4) and the solvent removed under reduced pressure. Chromatography of the residue (silica, 19:1 dichloromethane:methanol) gave the title compound as a white solid (0.036%q, 80%) . Mp 235°C (dec); NMR (DMSO) δ 7.82 (1H, d), 7.30-6.90 (11H, m), 6.85 (2H, d), 35 5.88 (1H, m), 4.86 (1H, d), 4.67 (1H, t), 3.67 (1H, m), 3.45 (1H, m), 2.75 (3H, m), 2.60 (1H, m), 2.43 (1H, m), 1.94 (1H, m)m), 1, 49 (2H, m), 0.73 (3H, d), 0.62 (3H; d); MS (CI) m/e 478 [M+H]+.

how sup a condition of the Example 74

Preparation of (2R.4S.5S.1'S)-5-(6-quinolinylmethyloxy-V 5 (carbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-V) (m ,yl)methyl-6-phenylmethyl-hexanamide

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Using the procedure of Example 34, except substituting (0 (E1) (6-quinolinylmethyl) - (4-nitrophenyl) carbonate for (4-2) (4-nitrophenyl) carbonate, the title compound was prepared.

Example 75

Preparation of (2R.4S.5S.1'S) -5- (benzoyl) amino-4-bydroxy-N
15 (1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenylmethyl-11
hexanamide

Timilar Square (E. 27 electric to broken quit gain all for the street of the street of

20 6-phenylmethyl-hexamide (1905)

(UE) 00 5 (L) The compound; of: Example 13(a) (0.11 g, 0.2 mmol),

together in dichloromethane (4 mL) at ambient temperature for 48hr. The solvent was removed under reduced pressure and the residue chromatographed (silica, 1:1 ethyl acetate:hexane) to

yield the title compound as a white solid (0.080 g, 61%).

6.69 (2H, s), 36.593 (1H, d), 6.373 (1H, d), 4.54 (2H, m), 3.68

30 (1H, t), 2.78 (2H, m), 2.66 (2H, m), 2.39 (1H, dd), 2.13 (1H, paize Jm), 1.625 (2H, pt), 0.87 (9H, s), 0.53 (3H, d), 0.48 (3H, d),

and - 4.0.02 & (3H, s), 40.000 (3H, s). Sixter a graph of the graph of

(135, Cisopropyl-1!-imidazol-2-yl) methyl-6-phenylmethyl-hexanamide
(15, Cisopropyl-1!-imidazol-2-yl) methyl-6-phenylmethyl-6-phenylmethyl-hexanamide
(15, Cisopropyl-1!-i

ammomium fluoride, 0.16 mL, 0.16 mmol, 1M solution in THF).

.10

After stirring at 40°C for 24 hr, the solvent was removed under reduced pressure and the residue was chromatographed (silica, step gradient, 1:1 ethyl acetate:hexane, 9:9:2 ethyl acetate:hexane:methanol) to give the title compound as a white solid (0.051 g, 79%). Mp.253-6°C; NMR (DMSO-d₆) δ 7.99 (1H, d), 7.91 (1H, d), 7.72 (2H, d), 7.750-7:02 (13H, m), 6.94 (2H, s), 4.83 (1H, br), 4.68 (1H, d), 4.14 (1H, m), 3.58 (1H, 2.d), 2.82.(4H, m); 2:49((1H, m); 1:92s(1H; m); 31.73)(1H, t), 1.40 (1H, m), 0.73 (3H, d), 0.63 (3H; d); MS (ES) m/e 539.2 $[M+H]^{+}$.

Example 76

Preparation of (2R.4S.5S.1'S)-5-(2-furvlcarbonvl)amino-4-15 hvdroxv-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-) phenylmethyl-hexanamide indicate and all

Following the procedure of Example 75(a), except using furoyl chloride in place of benzoyl chloride, the title compound was prepared as a white solid (0.019 g. 18%). Mp 212-3°C (dec); NMR (CDC13/CD3OD) $\delta_{8}7.46$ (1H, s), 67.30-6.88(12H, m), 6.85 (2H, s), 6.49 (1H, m), 4.48 (1H, d), 4.20 (1H, m), 3.67 (1H, m), 2.96 (4H, m) $\frac{1}{2}$ 2177 $\frac{1}{2}$ (2H, m), 2.58 (1H, d), (3H; d); (2.07 (1H, m), 1.71 (2H, m), 0.74 (3H; d); 0.65 (3H; d); ு MS(ES) m/e 528.32 [M+H]+.எ நிர்மாளிக்கிறிக்கி என்றுக்குக்க

or the content of the setting Example: 77.0 through the himse

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Preparation of (2R, 4S, 5S, 1'S) -5-(4-methoxybenzovl) amino-4hvdroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-30 phenylmethyl-hexanamide

old 1/25 gran to get a more in the verte ent diseviou sufficiently

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Following the procedure of Example 75(a), except using 4-methoxybenzoyl chloride in place@of@benzoyl@chloride, the title compound was prepared as a white solid (32%).

m), 6.80 (2H, m), 4.52 (1H, d); 4.516 (1H, m), 3.81 (3H, s), 3.62 (1H, d), 2.92 (2H, d), 2.72 (2H, m), 2.53 (1H, dd), 1.98 (1H, m), 1.73 (1H, m), 1.63 (1H \approx m), 0.712 (3H \approx d) \approx 10.62 (3H, d); MS(ES) m/e 569.4 [M+H]+. (1.1) (1.1) (1.1) (1.1) (2.1)

7°C (dec); NMR (CDCl3/CD3OD) & 7.64 (2H,2:d);, 7.22-6.87 (14H,

Lydude - Lady Surveyed, Example 78 (190.32 (19)

+8 Systematy-S-semination is figure and being executed as

Preparation of (2R, 4S, 5S, 1'S) -5-benzylcarbonyl) amino-4-

36.5 (jhydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-

900.7) phenylmethyl-hexamide. and the worldwise of average

Table (2R, 4S, 5S, 18) -5-benzylcarbonyl) amino-4-t-butyldimethyl

as: siloxy-N-(1!-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl

10 -hexanamide.aea call a transport to surface to the texture

Management of Example 75(a), except using a sphenylacetyl chloride in place of benzoyl chloride and

triethylamine in place of di(isopropyl)ethylamine, the title

COMPound was prepared as a white solid (20%). NMR (CDCl3) δ

15 27.40-6.75 ((19H, m), 5.40 (1H, d), 4.73 (1H, t), 4.41 (1H, q),

(4H, m), 1.61 (2H, m), 0.92 (6H, t), 0.77 (9H, s), 0.04 (3H,

s), 0.00 (3H, s).

pressure and the residue was chromatographed (silica, gradient, dichloromethane/methanol) to yield the title

COLUMN 17.38-7.06 (18H, m), (6.98 (2H, s), (4.72 (1H, d), 4.14 (1H, m),

(31, 30, 23, 67, (1H, m)), (34, (2H, s), 2.99, (4H, m), 2.67, (1H, m), 2.14)

 $\{(36,4)(2)(1H,5m),(1.87)(1H,5m),(51.63,(1H,5m),(0.94,(3H,4d),(0.79,(3H,5)),(3H,5m),(51.63,5),($

70.0 ((d); MS((ES) m/e 553.2)[M+H]+. gr (exig (en get get g

Example 79

#1 (35) - Compared to only the Association of (2R.4S.5S.1'S)-5-(4-hydroxybenzoyl) amino-4-

hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-

1998 Mphenylmethyl-hexanamide 1998 April 1998 1998

(3H, s).

a) (2R,4S,5S,1'S)-5-(4-acetoxyphenyl)-4-t-butyl dimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide.

The compound of Example 13 (a) (0.11 g, 0.2 mmol) was dissolved in dichloromethane (2 mL), and BOP reagent (0.089 g, 0.2 mmol), triethylamine (0.028 mL, 0.2 mmol) and 4-acetoxybenzoic acid (0.043 g, 0.24 mmol) were added. After stirring at ambient temperature overnight the solvent was removed under reduced pressure. The residue was chromatographed (silica, 49:1 dichloromethane:methanol) to give the title compound as a white solid (0.11 g, 78%).

NMR(CDCl₃) δ 7.53 (2H, d), 7.28-6.97 (13H, m), 6.83 (1H, d), 6.78 (2H, s), 6.44 (1H, d), 4.54 (2H, m), 3.72 (1H, dd), 2.79

15 (4H, m), 2.49 (1H, dd), 2.24 (3H, s), 2.20 (1H, m), 1.70 (2H, m), 0.91 (9H, s), 0.66 (3H, d), 0.57 (3H, d), 0.07 (3H, s), 0.02 (3H, s).

THE TOTAL BURNO BYTE !!

- b) (2R, 4S, 5S, 1'S)-5-(4-hydroxybenzoyl) amino-4-t-butyl

 -20) dimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6
 phenylmethyl-hexanamide (1) 2 100 mbjmi-1 1-100 mg/m/s
- The product from reaction 79(a) (0.11 g, 0.15 mmol) was dissolved in methanol (5 mL) and powdered potassium carbonate (0.12 g, 0.9 mmol) was added. After stirring the suspension vigorously for 2 h, the mixture was filtered and the solvent removed from the filtrate at reduced pressure. Chromatography of the residue (silica, 19:19:2 ethylacetate:hexane:methanol) gave the title compound as a white solid (0.066 g, 66%). NMR(CDCl3) 87.35 (2H, d), 7.24-6.98 (12H, m), 6.67 (4H, m), 6.32 (1H, d), 4.63 (2H, m), 3.76 (1H, dd), 2.78 (4H, m), 2.44 (1H, d), 2.12 (1H, m), 1.64 (2H, m), 0.88 (9H, s), 0.44 (3H, d), 0.32 (3H, d), 0.05 (3H, s), 0.01
 - 35 c) (2R, 4S, 5S, 1'S) -5-(4-hydroxybenzoyl) amino-4-hydroxy-N-(1'isopropyl-1'-imidazol-2-yl) methyl-6-phenylmethyl-hexanamide
 Following the procedure of Example 75(b), except using
 the compound of Example 79(b) in place of the compound of

Example 75(a), the title c mpound was prepared as a white solid (57%). Mp 267-8°C (dec); NMR(CDCl₃/CD₃OD) δ 7.57 (2H, COLL MILE d), 7.33-6.75 (17H, m), 4.48 (1H, d), 4.14 (1H, m), 3.58 (1H, d), 2.90(2H, m), 2.82(1H, m), 2.73(1H, m), 2.53(1H, dd), 2.04 (1H, m), 1.65 (2H, m), 0.73 (3H, d), 0.58 (3H, d); MS $(ES)_{M} = (ES)_{M} = (ES)_{M}$

11 hear out a flag. Example 80 place and

- Preparation of (2R.4S.5S.1'S)-5-(cinnamov1) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-vl)methyl-6-phenylmethyl-The manamide would be seen to be a seen to be a seen of the seen o
- m' Acamb a bFollowing the procedure of Example 75(a), except using cinnamoyl, chloride in place of benzoyl chloride, the title 15 compound was prepared as a white solid (25%). Mp 273°C; NMR (CDCl₃/CD₃OD), δ 7.55-6.91 (19H, m), 6.86 (2H, s), 6.53 (1H,
 - d), 4.37 (1H, d), 4.15 (1H, dt), 3.62 (1H, d), 2.91 (2H, m), (1.2.78)(2H, m), (2.59)(1H, dd), 2.04(1H, m), 1.76(1H, m), 1.65(1H, m), 0.79 (3H, d), 0.69 (3H, d); MS = (ES) m/e 565.2

bs:20@3[M+H]+. (for@ 01.6 ,ra 13) s - ceparth conjul to large as

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sectioners and bus before ser (see Example 81 / / eggs

embass Preparation of (2R.4S.5S.1'S)=5-(2-hydroxybenzovl) amino-4-

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(die phenylmethyl-hexanamide and been a id most decorolable

- ad .Fit 0: 3 Following the procedure of Example 79(a), except using 08.8 (2-acetoxybenzoic:acidfin place of 4-acetoxybenzoic acid, the title compound was prepared (50%) ... Mp 197°C; NMR (CD3OD) &
- 7.77 (1H, d), 7.42-6.78 (17H, m), 4.62 (1H, d), 4.32 (1H, -C-Loxsiddt), 3.710(1H, m), 2.94 (2H, m), 2.78 (2H, m); 2.57 (1H, m), 2.03 (1H, m), 1.84 (1H, m), 1.67 (1H, m), 0.82 (3H, d), 0.68 (3H, Ad); MS (ES) m/e 555.2 [M+H] +. Add a second

manageon and rat (a) Set becomens. In the managers of the E will be of Coforcial Military and a contraction of the contrac 30.5 (a) 19. (b) 20. (c) 30. (c) 45. (c) 45. (c) 46. (

(A) (B) (C), (A) (B) (P) (C) (B)

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Preparation of (2R,4S,5S,1'S)-5-(imidazoy)-4-yl-acetyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-

phenylmethyl-hexanamide (F. (B.)) (B.) (M. (M.)) (O) (C. (B.))

Following the procedure of Example 79(a) -79(c), except using (imidazol-4-yl) acetic acid in place of 4-acetoxy benzoic acid, the title compound was prepared.

TAIKS 10 A. TO A. TO THE STATE OF Example 83 Inches States III

Preparation of (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4-carbomethoxyethylimidazol-2yl) lmethyl-6-phenyl-2-phenylmethyl-hexanamide

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15

a) (1S) 1-carbobenzyloxyamino-1-isopropyl-1-[(4-(E-carbomethoxyethylene)imidazol-2-yl)]methane

The compound of Example 27(b) (100 mg, 0.33 mmol),
lithium chloride (28 mg, 0.66 mmol) and

trimethylphosphonoacetate (61 mg, 0.33 mmol) were dissolved
in anhydrous acetonitrile (2 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (55 mg, 0.36 mmol) was added and the reaction
mixture was stirred at room temperature overnight. The
solvent was removed under reduced pressure and the residue
was purified by flash chromatography (silicaa, 2% methanol/
dichloromethane to afford the title compound (72 mg, 61%).

NMR(CDCl3) δ 7.60-7.10 (6H, m), 6.50 (1H, br s), 6.10 (1H, br

2.30 (1H, br m), 1.10-0.80 (6H, m); MS m/e 358:2* [M+H] + 3

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Following the procedure of Example 1(b), except substituting the compound of Example 82(a) for the compound of Example 1(a), the title compound was prepared. NMR(CDCl3) δ 6.65 (1H, s), 4.40 (2H, br s), 3.82 (1H, d, J=3 Hz), 3.65 (3H, s), 2.90-2.55 (4H, m), 2.05 (1H, m), 0.90 (6H, d, J=3Hz).

c) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-carbomethoxyethylimidazol-2yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide

- Following the procedure of Example 1(c) except using the compound of Example 82(b), the title compound was prepared. NMR(CDCl3) δ 7.35-6.90 (12H, m), 6.55 (1H, s),
 - 4.75 (1H, d, J=4 Hz), 4.45 (1H, m) 3.95 (1H, m), 3.70 (3H,
- O: 4 р (S), 2.90-2.40 (9H, m), 1.90-1.60 (2H, m), 1.38 (9H, s),
 - 10 0.90-0.70 (15H, m), 0.10 (6H, d, J=2 Hz).

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- d) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N[1'-isopropyl-1'-(4-carbomethoxyethylimidazol-2-yl)]methyl-6phenyl-2-phenylmethyl-hexanamide.
 - Following the procedure of Example of 9(d) except using the compound of Example 83(c), the title compound was prepared. NMR(CDCl3) δ 7.30-6.90 (10H, m), 6.55 (1H, s), 5.00 (1H, d, J=4 Hz), 4.45 (1H, m), 3.70 (3H, s), 2.95-2.50 (9H, m), 2.25 (1H, m), 1.80-1.60 (2H, m), 0.85 (9H, s), 0.70 (6H, d, J=3 Hz); MS m/e 621.4 [M+H]⁺.

Les Roam : Bedoorda van Company . Example 84

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-425 hydroxy-N-[1'-isopropyl-1'-(4-carboxamidoimidazol-2yl) lmethyl-6-phenyl-2-phenylmethyl-hexanamide

- - Anhydrous hydrazine (47 μL, 1.5 mmol) was added to a solution of the compound of Example 26(b) (100 mg, 0.30 mmol) in anhydrous methanol. The resulting mixture was stirred overnight at room temperature and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and 10% aqueous Na₂CO₃ and the organic extract was dried over Na₂CO₃ and vaporated under reduced pressure. The residue
- was purified by flash chromatography (silica, 4% methanol/dichloromethane) to afford the title compound (52)

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mg, 52%). NMR(CD3OD) δ 7.50 (1H, s), 7.30-7.20 (5H, m), 5.00-4.90 (2H, m), 4.45 (1H, d, J=6 Hz), 2.10 (1H, br m), 0.95-0.75 (6H, m); MS m/e 332.2 [M+H]+

b) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-[(4-azidocarbonyl)imidazol-2-yl]methane

The compound of Example 83(a) was dissolved in 2N HCl (1 mL) and glacial acetic acid (0.2 mL) and cooled in an ice bath. A solution of sodium nitrite (11 mg, 0.16 mmol) in H2O (200 µL) was added dropwise. The reaction mixture was stirred for 0.5 h, neutralized with cold concentrated ammonium hydroxide and extracted with ethyl acetate. The organic extract was dried over Na2CO3 and the solvent removed in vacuo to yield the title compound (54mg, 100%).

NMR(CDCl3) & 7.75 (1H, s), 7.35-7.20 (5H, m), 5.20-5.00 (2H, m), 4.62 (1H, br m), 2.60 (1H br m), 1.10-0.80 (6H, m); IR 2123cm-1 (CON3).

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The compound of Example 83(b) was dissolved in 2 mL of ethyl acetate and stirred with of concentrated ammonium hydroxide (1 mL) at 0°C for 0.5 h, then at room temperature overnight. The reaction mixture was diluted with H₂O, extracted with ethyl acetate, and dried over Na₂CO₃. The solvent was removed in vacuo and the residue was purified by flash chromatography (silica, 4% methanol/ dichloromethane) to afford the title compound (50mg, 100%). NMR(CDCl₃) δ 7.45 (1H, s), 7.25-7.10 (5H, m), 5.00-4.85 (2H, m), 4.35 (1H, d, J=3 Hz), 2.00 (1H, br m), 0.90-0.70 (6H, m); MS m/e 317.2 [M+H]⁺.

d) (1S)-1-amino-1-isopropyl-1-(4-carboxamidoimidazol-2-yl) methane.

Following the procedure of Example 1(b), except substituting the compound of Example 83(c) for the compound of Example 1(a), the title comp und was prepared. NMR(CDCl3)

389 ((E) 80% 60 (Example 85)

δ 7.45 (1H, s), 3.47 (1H, d, J=3 Hz), 1.80 (1H, br m), 0.75-

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e) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-tbutyldimethylsiloxy-N-[1'-isopropyl-1'-(4carboxamidoimidazol-2-yl)]methyl-6-phenyl-2-phenylmethylde a hexanamide stack has to a start angle and the con-

of all the properties and every fine to the

Following the procedure of Example 1(c), except using the compound of Example 83(d), the title compound was 10 prepared. NMR(CDCl3) δ 7.50 (1H, s), 7.45-6.90 (11H, m), . . 12 6.25 (1H, d, J=4 Hz), 4.50 (1H, d, J=6Hz), 4.10 (1H, br m), (拍:) 3.60g(1H, m), 2.90-2.40 (5H, m), 1.90g (1H, br. m), 1.70-1.50 (2H, br(m), 1.35 (9H, s), 0.90 (9H, s), 0.70-0.60 (6H, m),10 (2 0.10 (6H, m) 10 (4H) (1E) (1E, S 44) (1E) (1E, S 45)

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(2R, 4S, 5S, 1'S) -5- (t-butoxycarbonyl) amino-4-hydroxy-N-[1'-isopropyl-1'-(4-carboxamidoimidazol-2-v1)]methyl-6phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 9(d) except using the 20 compound of Example 83(e) the title compound was prepared. 2.0 NMR (CD3OD) & 7.45 (1H, s), 7.25-6.85 (10H, m), 4.50 (1H, d, $(\text{Long}_4 \times \text{J=6}, \text{Hz}) \times 4.10 \times (1\text{H}, \text{m}) \times 3.60 \times (1\text{H}, \text{m}) \times 2.85-2.50 \times (5\text{H}, \text{m}) \times 2.00$ magaza(1H, br m) 31.80-1.50 (2H, m) 31.30 (9H, s), 0.80-0.65 (6H,

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Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(5-(1-oxopropyl)-2-thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide

a) (2R, 4S, 5S, 1'S)-2-phenylmethyl-4-t-butyldimethyl-siloxy-5thioureido-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl)) methylthe whexanamide and the house is recorded to the first part of a

A solution of benzoyl isothiocyanate (prepared from 35 ammonium thiocyanate (147 mg, 1.93 mmol) and benzoyl chloride (257 mg, 1.84 mmol) in of acetone (10 mL) according to the

procedure of J. Amer. Chem. Soc., 56, 1408 (1934)) treated with a solution of (2R, 4S, 5S, 1'S)-2-phenylmethyl-4-tbutyldimethylsiloxy-5-amino-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide (1.0 g, 1.83 mmol) in acetone. After 20 min at 23°C, the solvent was evaporated, and the residue was dissolved in diethyl ether. The ether extract was washed with water, dried, and the solvent was evaporated. This residue was dissolved in of MeOH (25 mL), treated with 2.5N NaOH (0.1 mL) and heated to 50°C for 30 The solvent was evaporated, and the residue was ^{©∴} 10 dissolved in EtOAc. The organic solution was washed with water, dried, and the solvent evaporated. The residue was chromatographed (silica, 5% MeOH/CHCl3) to yield the title compound (520 mg, 47%). NMR (DMSO) 8.7.80 (1H, d) 7.35 (1H, 15 d), 6.70-7.20 (15H, m), 4.69 (1H, t), 4.54 (1H, m), 3.78 (1H, m), 2.72-2.86 (3H, m), 2.54 (1h, dd), 2.42 (1H, dd), 2.04 (1H, m), 1.82 (1H, m), 1.30 (1H, m), 0.92 (9H, s), 0.86 (3H, m)d), 0.74 (3H, d), 0.15 (6H, d). (4) 28 (85 (48) --b-lyds on frogers, on a letter to be seen of figure (constitution) and the constitution of the constitut

b) dimethylformamidino derivative of (2R,4S,5S,1'S)-2-phenylmethyl-4-dimethyl-t-butyl silyloxy-5-thioureido-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl)) methyl-hexanamide A solution of the compound of Example 85(a) (122 mg, 0.2 mmol) and dimethylformamide dimethylacetal (26 mg, 0.22 mmol) in CHCl₃ (2 mL) was stirred at 23°C for 16 h. The solvent and excess reactant was removed under high vacuum, and the residue was chromatographed (Florisil®, 2% MeOH/CHCL₃) to yield the title compound (100 mg, 76%). NMR(CDCl₃) δ 8.82 (1H, s), 7.05-7.40 (12H, m), 6.76 (1H, br s), 6.60 (1H, d), 3.14 (3H, s), 3.05 (3H, s), 2.70-3.04 (4H, m), 2.40 (2H, m), 1.68 (2H, m),

c). (2R, 4S, 5S, 1'S)-2-phenylmethyl-4-dimethyl-t-butyl

35 silyloxy-5-(5-(1-oxopropyl)-2-thiazolyl)amiño) 6-phenyl-N(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide

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1.00 (9H, s), 0.80 (6H, dd), 0.14 (6H, d).

A solution of the compound of Example 85(b) (100 mg, 0.15 mmol); 1-bromo-2-butanone (25 mg, 0.165 mmol); and

triethylamine (33 mg, 0.165 mmol) in acetonitrile (10 mL) was heated at 80°C for 3.5 h. The solvent was evaporated, and the residue shaken with a mixture of diethyl ether and aqueous NaHCO3. The ether was seperated, washed with water, dried, and the solvent was evaporated. The residue was recrystallized from a mixture of CHCl3 and hexane to yield the title compound (59 mg, 57%). NMR(CDCl3) & 7.75 (1H, s), e.7.02-7.38s(10H, m), 6.88s(2H, m), 6.80 (1H, br s), 6.70 (1H, d), 6.60 (1H, d), 4.62 (1H, t), 3.96 (1H, m), 3.78 (1H, t), 2.82 (3H, m), 2.72 (2H, q), 2.54 (2H, m), 2.20 (1H, m), 2.04 (1H, m), 1.66 (1H, m), 1.15 (3H, t), 0.96 (9H, s), 0.72 (6H, t), 0.10 (6H, d).

15 oxopropyl)-2-thiazolyl) amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl)) methyl-hexanamide

A solution of the compound of Example 85(c) (50 mg, 0.07 mmol) in (2 mL) of THE was treated with) of tetrabutyl-ammonium fluoride (0.2 mL, 1N solution in THF) 58°C for 1 h.

The solvents were evaporated, and the residue dissolved in ether. The ether was washed with water, dried, and the solvent evaporated. The residue was chromatographed (neutral alumina, Activity, V, impurities removed with 2% MeOH/EtOAc,

25 compound (22 mg, 55%). NMR(DMSO) δ 7.75 (1H, s), 7.66 (1H, d), 6.80-7.30 (13H, m), 4.93 (1H, br s), 4.78 (1H, t), 3.78 (1H, m), 3.68 (1H, dd), 3.00 (1H, dd), 2.92 (1H, dd), 2.86 (1H, m), 2.80-2.90 (1H, br), 2.76 (2H, q), 2.56 (2H, m), 2.12 (1H, m), 1.74 (1H, m), 1.69 (1H, m), 1.20 (3H, t), 0.80 (3H,

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Example 86 garage and all

Preparation of (2R.4S.5S.1'S) -2-phenylmethyl-4-hydroxy-5-(5-35 (1-oxopropyl)-2-thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide

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a) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-dimethyl-t-butyl silyloxy-5-(2-thiazolylamino) -6-phenyl-N-(1'lisopropyl-1'' (imidazo-2-yl)) methyl-hexanamide.

The compound of Example 85(a) (50 mg, 0.08 mmol) in CHCl3 (2 mL) was treated with chloroacetaldehyde (50 mg, 0.64 mmol). After 20 min the solvent and excess reagent were evaporated. The residue was dissolved in EtOAc, washed with aqueous NaHCO3, dried and the solvent evaporated. The residue was chromatographed (Florisil®, 60% EtOAc/hexane) to yield the title compound (42 mg, 83%). NMR(CDCl3) & 7.12-7.30 (10H, m), 7.02 (1H, d), 6.92 (2H, m), 6.82 (1H, br), 6.62 (1H, br), 6.38 (1H, d), 5.86 (1H, br), 4.58 (1H, t), 4.00 (1H, m), 3.86 (1H, m), 2.85 (3H, m), 2.52 (2H, m), 2.26 (1H, m), 2.16 (1H, m), 1.68 (1H, m), 0.98 (9H, s), 0.70 (6H, t), 0.12 (6H, d).

- b) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(5-(1-oxopropyl) -2-thiazolyl) amino) -6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl)) methyl-hexanamide.
- 20 Following the procedure of Example 85(d), except substituting the compound of Example 86(a) for the compound of Example 85(c), the title compound was prepared.

 NMR(CDCl₃/DMSO) δ 6.80-7.42 (14H, m), 6.40 (2H, m), 5.18 (1H, br), 4.74 (1H, t), 3.70 (1H, m), 3.62 (1H, m), 3.00 (2H, m), 2.88 (2H, m), 2.58 (1H, m), 2.18 (1H, m), 1.80 (2H, m), 1.72 (6H, dd).

Example 87 (400.5 (4 31)

(34, 400 (E) #8.6 (b) (H)

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- Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(5-propyl-2-thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide
- a) (2R, 4S, 5S, 1'S)-2-phenylmethyl-4-t-butyldimethylsilyloxy-5-35 (5-propyl-2-thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide.

A solution of the compound of Example 85(a) (120 mg, 0.2 mmol) in CHCl₃ (5 mL) was treated with 2-bromovaleraldehyde

(100 mg, 0.6 mmol) and warm d to 60°C for 30 min and 80°C for 5 min. The solvent and excess reagent were removed under reduced pressure. The residue was dissolved in EtOAc, washed with aqueous K₂CO₃, dried, and the solvent evaporated. The residue was chromatographed (silica, 3% MeOH/CHCl₃) to yield the title compound (55 mg, 41%). NMR(CDCl₃) & 7.10-7.30 (10H, m), 6.88 (2H, m), 6.72 (1H, br), 6.68 (1H, s), 6.60 (1H, br), 5.60 (1H, br), 4.62 (1H, t), 3.94 (1H, m), 3.78 (1H, t), 2.82 (3H, m), 2.50 (4H, m), 2.26 (1H, m), 2.04 (1H, m), 1.66 (1H, m), 1.55 (2H, sextet), 0.94 (9H, s), 0.92 (3H, t), 0.70 (6H, dd), 0.08 (6H, d).

b). (2R, 4S, 5S, 1'S)-2-phenylmethyl-4-hydroxy-5-(5-propyl-2-thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide.

Following the procedure of Example 85(d), except substituting the compound of Example 87(a) for the compound of Example 85(c), the title compound was prepared. NMR(CDCl₃) δ 7.50 (1H, br), 6.90-7.24 (10H, m), 6.78 (2H, s), 6.60 (1H, s), 6.18 (1H, br), 5.76 (1H, br), 4.60 (1H, t), 3.68 (1H, m), 3.52 (1H, m), 3.05 (1H, dd), 2.95 (2H, m), 2.82 (1H, dd), 2.62 (1H, m), 2.58 (2H, t), 2.32 (1H, m), 1.86 (2H, m), 1.60 (2H, sextet), 0.96 (6H, t), 0.75 (6H, dd).

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Example 88

Preparation of (2R.4S.5S.1'S)-5-(nicotinyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide

Following the procedure of Example 75(a), except using nicotinoyl chloride in place of benzoyl chloride, the title compound was prepared as a white solid (43%). Mp 233-4°C (dec); NMR(CDCl₃/CD₃OD) δ 8.81 (1H, d), 8.59 (1H, dd), 7.99 (1H, m), 7.35-6.86 (14H, m), 6.79 (2H, s), 4.44 (1H, d), 4.19 (1H, dt), 3.59 (1H, m), 2.90 (2H, d), 2.68 (2H, m), 2.52 (2H, m), 1.96 (1H, m), 1.71 (1H, m), 1.58 (1H, m), 0.70 (3H, d), 0.58 (3H, d); MS(ES) m/e 540.2 [M+H]⁺.

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The above description fully discloses how to make and
                                                   use the present invention. However, the present invention is
     not limited to the particular embodiments described;
                              hereinabove, but includes all modifications thereof within
            175 the scope of the following claims: 450 do 280 stables at
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What, is claimed is:

The Acompound of the formula (I):

ones (DY \mathbb{R}^3) in a service was at \mathbb{R}^3 (1) to \mathbb{R}^3 as \mathbb{R}^3 (2) and \mathbb{R}^3 (3) and \mathbb{R}^3 (3) and \mathbb{R}^3 (4) and \mathbb{R}^3 (5) and \mathbb{R}^3 (6) and \mathbb{R}^3 (7) and \mathbb{R}^3 (7) and \mathbb{R}^3 (8) and \mathbb{R}^3 (1) and \mathbb{R}^3 (2) and \mathbb{R}^3 (3) and \mathbb{R}^3 (3) and \mathbb{R}^3 (4) and \mathbb{R}

value_park_new_c solv seq (I)
wherein:

wherein:

R¹ and R³ are each independently Q, Q-C₁₋₆alkyl,
Q-C₂₋₆alkenyl, Q-C₂₋₆alkynyl or C₁₋₆alkyl substituted by one
to five fluorine atoms, each optionally substituted by R²³;
Q is H, C₃₋₆cycloalkyl, C₅₋₆cycloalkenyl, Ar or Het

R² is H or OH; R⁴ is R⁶-NR¹¹- or CONR¹¹CHR⁶R⁷; R⁵ is R⁶-NR¹¹- or R¹⁰-NR¹¹-;

15 R6 is N R8,

x is NR11; O or S;

R⁷ is Q, Q-C₁₋₆alkyl or Q-C₂₋₆alkenyl;

R⁸ and R⁹ are each independently H, OH, halo, NO₂, COR¹², CF₃, Ar, C₁₋₆alkyl-R¹⁵, or R¹⁷(R¹⁸R¹⁹C)_m, or together form a fused C₂₋₄alkylene, aryl or heteroaryl moiety;

 R^{10} is A-(B)_n-;

R¹¹ is H or C₁₋₄alkyl;

R12 is R7, OR7, NR7R11 or an amino acid or amino alcohol;
B is an amino acid;

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rec25dilw has Alis H, Ar, Het, R17 (R18R19C) m, Ar-W, Het-W or

R17 (R18R19C) m-W, or phthaloyl each optionally substituted by one to three groups chosen from R15 or C1-6alkyl-R15;

W is C=0, OC(=0), $NR^{11}C(=0)$, SC(=0), $NR^{11}C(=S)$, SO_2 , $NR^{11}SO_2$ or P(=0) (OR^{22});

C=OR²², CO₂R²², CON(R¹⁶)₂, N(R²²)₂, NHC(=N)NH-A, I, Br, Cl, F, OR¹⁰, or OH, provided that when R¹⁵ is a substituent of the carbon adjacent to W, R¹⁵ is not halogen or OH when W is OC(=O) or NHCO;

35 R^{16} is H or C_{1-6} alkyl;

15

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25

R17, R18 and R19 are independently: i) H, R15 or C_{1-4} alkyl, C_{2-6} alkenyl, phenyl, naphthyl, C_{3-6} cycloalkyl or Het, each optionally substituted by one to three R15 or $R^{15}-C_{1-6}$ alkyl groups, or ii) R^{17} is as above and $(R^{18}R^{19}C)$ are joined together to form a phenyl, naphthyl, C3-6cycloalkyl or Het ring, or iii) R17 is as above and R18 and R19 together are =0;

 R^{22} is H, C_{1-6} alkyl, phenyl or phenyl- C_{1-4} alkyl; R^{23} is $-X'-(CH_2)_qNR^{24}R^{25}$, $X''[((CH_2)_rO)_s]R^{26}$, CH_2X "[((CH_2) $_rO$) $_s$] R^{26} , or benzofuryl, indolyl, azacycloalkyl, azabicyclo C7-11cycloalkyl or benzopiperidinyl, optionally substituted with C1-4alkyl; a smode wat on a wall of

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q is 2-5;

s is 1-6 and r is 1-3 within each repeating unit s; X' is CH2, O, S or NH;

X" is CH2, NR', O, S, SO or SO2;

 R^{24} and R^{25} are i) C_{1-6} alkyl, optionally substituted by OH, C1-3alkoxy, or N(R')2, ii) the same or different and joined together to form a 5-7 member heterocycle containing up to two additional heteroatoms selected from NR, O, S, SO, SO2, said heterocycle optionally substituted with C1-4alkyl, iii) aromatic heterocycle, optionally substituted with C1-4alkyl or N(R')2;

R' is H or C₁₋₄alkyl;

;一点(每)一次(分表)(0.5) R^{26} is H, C₁₋₄alkyl, C(=0) R^{27} , C(=0) $U[(CH_2)_mO]nR^1$, $P (=0) (OM)_2$, CO_2R^{27} , $C (=0) NR^{27}R^{28}$, where M is a mono or divalent metal ion, and U is NR or O; as as a

R27 is C1-6alkyl, or Ar, optionally substituted with one or more hydroxy, carboxy, halo, C1-3alkoxy, CONR'2, NR'2, CO2R', SO2NR'2, CH2NR2, NR'COR', NR'SO2R', X"[(CH2)rO]sR' or CH2X"[(CH2)rO]sR'; S Constant (Certal Ones al M

 R^{28} is H, C_{1-6} alkyl or together with R^{27} forms a, 5-7. membered heterocycle or a 6 membered heterocycle containing a heteroatom selected from N, O and S; 00 1009.05 1000000

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or a pharmaceutically acceptable salt thereof. 30

2. A compound according to claim 1 wherein:

R1 and R3 are C1-6alkyl, Ar-C1-6alkyl, Ar-C2-6alkenyl,

Ar-C2-6alkynyl, or C1-6alkyl optionally substituted by one to

5 PA to complement

R4 is CONR¹¹CHR⁶R⁷;

None of the R⁵ is R¹⁰-NR¹¹; where the R⁵ is H, C₁-6alkyl, C₃-6cycloalkyl, phenyl or benzyl; R⁸ is H, C₁-6alkyl, COR¹², NO₂ or Br;

- (varchours) R9 is H, NO2, Br, COR12, CF3, Ar, C1-6alkyl, or C1-6alkyl-R15, wherein R12 is H, C1-6alkyl, Ar, OC1-6alkyl, NH2, and R15 is OH;

-(Lynch Canya on A is H, Het, R¹⁷ (R¹⁸R¹⁹C) m-W or Het-W; a colling ablam B is absent gor Val; a shirt ' and the year of the same and the colling and the colling absent gor val; as absent gor val;

R17, R18 and R19 are H, or C1-4alkyl, Het or Ar, each cycloptionally substituted by one or two R15 or R15C1-6alkyl groups, or (R18R19C) are joined together to form a phenyl, C3-6cycloalkyl or Het ring; and to have a shape and the state of the state of

- ((quodinapyxout) (composite - 'ingress (composite c

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- 3. A compound according to claim 1 wherein R4 is a CONR 1 CONR 1 CHR 6R7 and X is N-H. The contract of the con
- 4. A compound according to claim 3 wherein R⁸ is H and R⁹
 -25 3 is H or COR¹². The Cyclor is the latter of the Cord of t
 - 5. A compound according to claim 4 wherein R^7 is C_{1-6} alkyl.
- 30 R³ is benzyl, 4-hydroxy-benzylfor phenylpropenyl, de so while the second s
- 7. (A) compound according to claim 3 wherein A is R¹⁷ (R¹⁸R¹⁹C)_m-W, and R¹⁷, R¹⁸ and R¹⁹ are H, or C₁₋₄alkyl, Het -111 or Ar. In the second the advantage of the second to the second
 - 8. A compound according to claim 3 wherein B is absent and A is C₁₋₆alkylOC(=0).

- 9. A compound according to claim 3 wherein W is C=0.
- 10. A compound according to claim 1 wherein the compound is: (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)-

on the species of the base in

- - (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl) amino-6-phenyl-N-[1'-isopropyl-1'-(4-aminocarbonyl-thiazo-2-yl)]methyl-hexanamide;
- 10 (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl) amino-6-phenyl-N-[1'-isopropyl-1'-(thiazo-2-ÿ1)]methylhexanamide;
 - (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)-amino-6-phenyl-N-(1'-imidazo-2-yl)methyl-hexanamide
- (15 hydrochloride; the war to be ever 特別 base 計算 (作項)
 - (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl) amino-6-phenyl-N-[1'-methyl-1'-(imidazo-2-yl)] a methylhexanamide hydrochloride; to define for fyriten for the context of the contex
- amino-6-phenyl-N-[1'-benzyl-1'-(imidazo-2-yl)]methylhexanamide hydrochloride;
 (2R, 4S, 5S, 1'S)-5-(carbobenzyloxy)amino-4-hydroxy-N-(1'isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethylhexanamide;
- 25 (2R, 4S, 5S, 1'S)-5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1"-isopropyl-1'-(4, 5-dimethyl) imidazol-2-yl] methyl-6-phenyl-2-
- (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-isopropyl-1'-(N'-methyl) imidazol-2-yl]methyl-6-phenyl-2
 - phenylmethyl-hexanamide; onlyd-lexanamide; (2R, 4S, 5S, 1'S)-5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-(3-phenylpropargyl) hexanamide; (2R, 4S, 5S, 1'S)-5-(isopropoxycarbonyl) amino-4-hydroxy-N-(1'-
 - isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethylhexanamide; is a companie to the accompanie of the companies of th

"可有特殊的的性性"的。第35 第5

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- (2R,4S,5S,1'S)-5-(benzyloxyethoxycarbonyl) amino-4-hydroxy-N-
-Selvente (1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
         phenylmethyl-hexanamide;
     (2R, 4S, 5S, 1'S) -5- (methoxycarbonyl) amino-4-hydroxy-N-(1'-
 is go 5 isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
         hexanamide;
                                   to Dilegran
        (2R, 4S, 5S, 1'S) -5- (ethoxycarbonyl) amino-4-hydroxy-N-(1'-
  isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
         hexanamide;
   10 : (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
        isopropyl-1*-imidazol-2-yl)methyl-6-phenyl-2-(3-phenyl-2-
        propenyl) hexanamide; was a second of the second
   (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
     isopropyl-1'-(4-nitroimidazol-2-yl)]methyl-6-phenyl-2-
        phenylmethyl-hexanamide;
                                    ar are ma
   -- (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
    ethyl-1!-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
        hexanamide;
                           irt.
   - (2R, 4S, 5S, 1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-(1'-
  20 propyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
       hexanamide;
                           solutionary so the solution
   (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'-
  isopropyl-1'-(4-bromoimidazol-2-yl)]methyl-6-phenyl-2-
       phenylmethyl-hexanamide;
                                    The state of the
   25 (2R, 4S, 5S, 1'S) -5- (t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
 -- Legis isopropyl-1'-(4,5-dibromoimidazol-2-yl)]methyl-6-phenyl-2-
       phenylmethyl-hexanamide;
   (2R, 4S, 5S, 1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'-
       isopropyl-1:-(4-methylimidazol-2-yl)]methyl-6-phenyl-2-
      phenylmethyl-hexanamide;
   (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'-
      isopropyl-1'-(4-trifluoromethylimidazol-2-yl)]methyl-6-
      phenyl-2-phenylmethyl-hexanamide;
                                                (2R, 4S, 5S, 1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-methyl-
      N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
      phenylmethyl-hexanamide;
```

```
(2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
              isopropyl-1'-(4-carbomethoxyimidazol-2-yl)]methyl-6-phenyl-2-
                                                                        TO ALCHARDAD ALCAD
             phenylmethyl-hexanamide;
              (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
      5 isopropyl-1'-(4-methylcarbonylimidazol-2-y1)]methyl-6-phenyl-
             2-phenylmethyl-hexanamide;
                                                                                                   Apple an apr
             (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
             isopropyl-1'-(4-isopropylcarbonyl-imidazol-2-yl)]methyl-6-
            phenyl-2-phenylmethyl-hexanamide;
           (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
   10
           isopropyl-1'-(4-phenylcarbonyl-imidazol-2-yl)]methyl-6-
            phenyl-2-phenylmethyl-hexanamide; bissociak in the recognition of the phenylmethyl-hexanamide;
           (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
        isopropyl-1'-(4-formylimidazol-2-yl)]methyl-6-phenyl-2-
           phenylmethyl-hexanamide;
                                                                        CALL OF THE A SHOP OF THE PARTY OF THE PARTY
            (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
       isopropyl-1'-(4-(hydroxymethyl)-imidazol-2-yl)]methyl-6-
           phenyl-2-phenylmethyl-hexanamide;
       (2R, 4S, 5S, 1'S) -5- ((tetrahydrothiopyran-4-yl)oxycarbonyl)-
           amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
  20
           phenyl-2-phenylmethyl-hexanamide;
           (2R, 4S, 5S, 1'S) -5-((tetrahydro-4H-pyran-4-yl)oxycarbonyl)-
        amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
          phenyl-2-phenylmethyl-hexanamide; saa xed digram gift hear
 25 (2R, 4S, 5S, 1'S) -5- (4-picolinyloxy) amino-4-hydroxy-N-(1'-
         isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
          hexanamide:
                                                                         Cabrell and College Section
          (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
        isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(4,4,4-
         trifluorobut-1-yl) hexanamide ; signmersa-bylanci jada
       (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
         isopropyl-1'-(4-((1RS)-1-hydroxyethyl)-imidazol-2-yl)]methyl-
         6-phenyl-2-phenylmethyl-hexanamide; samiyabilg-f, algaba q
         (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-(1-
         methyl)propyl-1'-(imidazol-2-yl)]methyl-6-phenyl-2-
35
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phenylmethyl-hexanamide;

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(2R, 4S, 5S, 1'S) -5-(propylaminocarbonyl) amino-4-hydroxy-N-[1'-
                   isopropyl-1'-(imidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-
                   hexanamide;
                                                        the of the map of the straining the
        ---------(2R, 4S, 5S, 1'S) -5-(4-hydroxybutanoyl) amino-4-hydroxy-N-(1'-
                   isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
                   phenylmethylhexanamide;
                   (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(benzyloxy-
              carbonyl)valylamino-6-phenyl-N-(1'-isobutyl-1'-imidazo-2-
                   yl) methyl-hexanamide:
                                                                               S. E. William St. David Co.
   The second of the second secon
                amino-6-phenyl-N-(1'-isobutyl-1'-imidazo-2-yl)methyl-
                  hexanamide:
                   (2R, 4S, 5S, 1'S) -5-[(imidazol-2-yl)methyloxycarbonyl]amino-4-
    hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
                  phenylmethyl-hexanamide;
  VN CERT (2R, 4S, 5S, 1'S, 1"RS) -5-((1"-(imidazol-2-yl)-2"-methyl)-
                 propyloxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-
                 imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide;
  (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
  weisopropyl-1;-(4-(imidazol-2-yl)imidazol-2-yl)]methyl-6-
m(E)-Wewgaphenyl-2-phenylmethyl-hexanamide;
  toble and (2R, 4S, 5S, 1'S) -5-(1-oxo-thian-4-yl) oxycarbonyl) amino-4-
   hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
      49 msphenylmethylhexanamide; 2000 to Section to the first
     25 2 (2R, 4S, 5S, 1'S) -5- ((tetrahydrosulfonylpyran-4-
               'yl) oxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-
               yl)methyl-6-phenyl-2-phenylmethylhexanamide; A stori
          (2R, 4S, 5S, 1 S) -5-((1, 1-dimethyl-2-(benzyloxycarbonyl-
white glycyloxy) ethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-
   - 130 coming imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide
             phydrochloride salt; is ( typical and date tell your of ty)
                (2R, 4S, 5S, 1'S) -5-((1, 1-dimethyl-2-glycyloxy) ethoxycarbonyl) -
             - amino-4-hydroxy-N-(14-isopropyl-14-imidazol-2-yl)methyl-6-
      www.mphenyl-2-phenylmethyl-hexanamidedihydrochloridesalt;
       35 or(2R, 4S, 5S, 1'S) -5- ((1-acetyl) amino-4-hydroxy-N-(1'-isopropyl-
             · 1'-imidazol-2-yl)methyl-6-ph nyl-2-phenylmethylhexanamide;
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(2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
 [velident] isopropyl-1'imidazol-2-yl)methyl-6-phenyl-2-(4-4) as
                                                Lebiniens, an
        benzyloxyphenylmethyl) hexanamide;
        (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
        hydroxyphenylmethyl) hexanamide; it saykodi (dd mal ya. de
        (2R, 4S, 5S) -5-(t-butoxycarbonyl) amino-4-hydroxy-2- (1)
        phenylmethyl-6-phenyl-N-[1'-cyclopropyl-1'-imidazol-2-
        yl]methyl-hexanamide;
                                       tal decomposed tel vel fore 19
 10 (2R, 4S, 5S, 1'S) -5- ((isopropylthiol) carbonyl) -amino-4-hydroxy-
        2-phenylmethyl-6-phenyl-N-[1-isopropyl-1:-imidazol-2-
        yl]methyl-hexanamide;
                                                 hera arrea
 (2R, 4S, 5S, 1'S) -5-[3-(1H-imidazol-2-yl)-3-hydroxy-4-)
      methylpentylamido]-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-
        yl) methyl-6-phenyl-2-phenylmethyl-hexanamide; granter
     (2R, 4S, 5S, 1'S) -5-[(4-methoxyphenoxy)carbonyl]amino-4-hydroxy-
        N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
    phenylmethyl-hexanamide; you don't want was live's do so all
        2R, 4S, 5S, 1'S) -5- (t-butylaminocarbonyl) amino-4-hydroxy-N-(1'-
   20 isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
        (2R, 4S, 5S, 1'S) -5- (methylaminocarbonyl) -amino-4-hydroxy-N-(1'-
       isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
        (2R, 4S, 5S, 1'S) -5-phenylaminocarbonyl) amino-4-hydroxy-N-(1'-
        isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide;
        (2R, 4S, 5S, 1'S) -5-N-(propylaminocarbonyl) amino-4-hydroxy-N-
 (1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-
       (2R, 4S, 5S, 1'S) -5- (n-propylaminothiono) amino-4-hydroxy-N-
       (1'isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide;
       2R, 4S, 5S, 1'S) -5- (isopropylaminocarbonyl) -amino-4-hydroxy-N-
       (1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-
       hexamide; 2. 12. 10-8 lydgama > 1/2, 1-6-(8-2, 20, 12-45)
       (2R, 4S, 5S, 1'S) -5- (aminocarbonyl) amino-4-hydroxy-N-(1'-
       isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide;
35 (2R, 4S, 5S, 1'S) -5-(6-quinolinylmethyloxy-carbonyl) amino-4-
 hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
       phenylmethyl-hexanamide;
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(2R, 4S, 5S, 1'S) -5- (benzoyl) amino-4-hydroxy-N-(1'-isopropyl-1'-
                     imidazol-2-yl)methyl-6-ph nylmethyl-hexanamide;
                     (2R, 4S, 5S, 1'S) -5- (2-furylcarbonyl) amino-4-hydroxy-N- (1'-
         isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
   11- (2R, 4S, 5S, 1'S) -5- (4-methoxybenzoyl) amino-4-hydroxy-N- (1'-
                   isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
                    (2R, 4S, 5S, 1'S) -5-benzylcarbonyl) amino-4-hydroxy-N-(1'-
            ____isopropyl-1!-imidazol-2-yl)methyl-6-phenylmethyl-hexamide;
              old(2R, 4S, 5S, 1'S) -5-(4-hydroxybenzoyl)amino-4-hydroxy-N-(1'-
                   isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
                    (2R, 4S, 5S, 1'S) -5-(cinnamoyl) amino-4-hydroxy-N-(1'-isopropyl-
           bas 1 - imidazol-2-yl) methyl-6-phenylmethyl-hexanamide;
                    (2R, 4S, 5S, 1'S) -5-(2-hydroxybenzoyl) amino-4-hydroxy-N-(1'-
           isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
 VIH | 15 | (2R, 4S, 5S, 1 'S) -5 - (imidazoyl-4-yl-acetyl) amino-4-hydroxy-N-
   5 do Jan (1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenylmethyl-
                   hexanamide;
                                                                of mir to so to a sole the con-
                   (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'-
             ed isopropyl-17-(4-carbomethoxyethylimidazol-2-yl)]methyl-6-
          20 phenyl-2-phenylmethyl-hexanamide; ###
                                                                                                and the Williams
                   (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
                  isopropyl-1'-(4-carboxamidoimidazol-2-yl)]methyl-6-phenyl-2-
                  phenylmethyl-hexanamide;
                  (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(5-(1-oxopropyl)-2-
                 thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-
                 yl)) methyl-hexanamide;
                  (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(5-(1-oxopropyl) -2-
                 thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-
 eq bern (yl)) methyl-hexanamide; we down to be a second of the control of the con
.f ad: 30 for (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(5-propyl-2-
                thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-
                 yl))methyl-hexanamide; and francki to brunker and k = 101
                 (2R, 4S, 5S, 1'S) -5- (nicotinyl) amino-4-hydroxy-N-(1'-isopropyl-
                 1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide.
        35
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11. A compound according to claim 1 which is (2R, 4S, 5S, 1'S) - . 5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'-isopropyl-1'-(4-

phenylmethyl-hexanamide on the data (or finite about the content of the content

12. A compound according to claim 1 which is (2R, 4S, 5S, 1'S)
2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl) -amino-6-phenyl
N-(1'-isopropyl-1'-(imidazo-2-yl)) methyl-hexanamide.

according to Claim 1 and a pharmaceutically (acceptable carrier.

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according to Claim 1 and an oil () d-(10,000,000)

(Ref. 139, 38, 187 - 5- Beliefer on a line of the contract

- 15 15. A method of treating disease states associated with HIV infection comprising administering an effective amount of a compound according to Claim 1.
 - 16. The use of a compound according to Claim lain the
 20 manufacture of a medicament.

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we see 17. A compound of the formula: A book to de good the

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wherein Pr^2 is an amino protecting group, and R^{7} , R^{8} and R^{9} are as defined in Claim 1 with any reactive groups protected.

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30 18. A compound of formula: A COMPANY MARKET WAS TEXT

$$R_1$$
 R_2 R_4 R_4 R_6 R_6

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wherein:

R₁ and R₃ are ach independently C₁₋₆alkyl,

Ar-C₁₋₆alkyl, H t-C₁₋₆alkyl, C₂₋₆alkenyl, Ar-C₂₋₆alkenyl,

Het-C₂₋₆alkenyl, C₃₋₆cycloalkyl-C₁₋₆alkyl or

C₃₋₆cycloalkenyl-C₁₋₆alkyl;

or the Ramisa Hoor OH; ground our tell to a light

R4 is R6-NH-, or NH R6 10 NH;

R5 is R6-NH- or R10-NH;

R6 is

wherein:

10

X is NR_{11} , O_{1} or $S_{1} \otimes \cdots \otimes V_{N}$

Rillis Hor C1-3alkyl;

Rg and Rg are each independently H, OH, halo, acyl,

or substituted alkyl;

or R6 is C

15 wherein: kaller factor in the miles age.

X is NH, O, or S;

moiety; is a fused C2-4 alkylene, aryl or heteroaryl

R7 is C1-6alkyl, Ar-C1-6alkyl, Het-C1-6alkyl,

C2-6alkenyl, Ar-C2-6alkenyl, Het-C2-6alkenyl,

C3-6cycloalkyl-C1-6 alkyl or C3-6cycloalkenyl-C1-6alkyl;

R10 is a moiety A-(B)_n-, where n = 0 or 1; and B is, independently, an α-amino acid chosen from the group: Ala, Asn, Cys, Trp, Gly, Gln, Ile, Leu, Met, Phe, Pro, Ser, Thr,

Tyr, Val, His, or trifluoroalanine, wherein the amino group of B is bonded to A and the carboxy group of B is bonded to the structure;

A is covalently attached to the amino group of the adjacent residue B or to the amino group of the structure if

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- 1) trityl,
- 2) hydrogen,
- turni t at 83) as C126alkyl, fortodice e e e e ett
 - (4) R14-CO-wherein R14 is:

	•	hydrogen; do one go boa go
	b)	C1-6alkyl, unsubstituted or substituted with
		one or more hydroxyl groups, chlorine atoms,
		or fluorine atoms, Priviled to to you go
. 5	c)	phenyl or naphthyl unsubstituted or
•		substituted with one or more substituents R15
		wherein R15 is:
		Cl-4dikyi, an interest the control of
		11/ nalogen, where halogen is F, CI, Br or
10		
	•	iii) hydroxyl,
		iv) nitro, tidental
		v) C1-3alkoxy, or me and a
		vi) -CO-N(R16)2 wherein R16 is,
15		independently, H or C1-4alkyl; or
· .	d)	a 5-7 member heterocycle such as pyridyl,
		furyl, or benzisoxazolyl;
		haloyl wherein the aromatic ring is
		ubstituted or substituted with one or more
20		stituents R ₁₅ ;
1 42° 0	5426); IR <u>1</u> 7	(R18R19C) m-CO- wherein m = 1-3 and R17, R18,
		R ₁₉ are independently:
	Syr (3) (2) a) 5	hydrogen, of a say to a light of the say of
		chlorine or fluorine, sa sayous sages o.
		C ₁₋₃ alkyl unsubstituted or substituted with
		one or more chlorine or fluorine atoms or
		hydroxyl groups, and help ne ne getting
$_{A}\otimes \mathcal{A}_{A}^{\ast }\otimes \mathcal{A}_{A}^{\ast }$	d) (hydroxyl, and a society of the socie
grown of the	% (a) (e) (y	phenylmor naphthyl unsubstituted organization
G. 30		substituted with one or more substituents R15,
·	f)	C1-3alkoxy,
	g)	a 5-7 member heterocycle, or
il sur to gro) - (h)	R17, R18, and R19 may be independently joined
· ·	-	to form a monocylic, bicyclic, or tricycle
35		ring system each ring of which is C3-6
		cycloalkyl; Asygunyi (S
-	7) R ₁₇ (I	$R18R19C)_{m}-W-$ wherein $m = 1-3$ and W is OCO or

SO2 and R17, R18, and R19 are as defined above,

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The second secon

except R17, R18, and R19 are not chlorine, fluorine or hydroxyl if th y are adjacent to W;

- 8) R20-W-wherein R20 is a 5-7 member heterocycle such as pyridyl, furyl, or benzisoxazolyl;
- 9) R21-W- wherein R21 is phenyl or naphthyl unsubstituted or substituted with one or more subsituents R₁₅;
 - 10) R17-(R18R19C)m-P(0) (OR22) wherein R22 is C1-4 alkyl or phenyl;
 - 11) R₂₀-P O) (OR₂₂)-; or
 - R₂₁-P(0)(OR₂₂)-;

and any average or pharmaceutically acceptable salt thereof.

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INTERNATIONAL SEARCH REPORT

IPC(CLASSIFICATION OF SUBJECT MATT 5) :CO7D 233/64, 263/32, 277/30; A61K 3 CL :Please See Extra Sheet.	01/415, 31/42, 31/425
В.	FIELDS SEARCHED	4.0
Minim	m documentation searched (classification sys	tem followed by classification symbols)
U.S.	: Please See Extra Sheet.	Application of the following of the contraction of
Docum	entation searched other than minimum docume	ntation to the extent that such documents are included in the fields searched
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		n, where appropriate, of the relevant passages (1) Relevant to claim
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Fur	her documents are listed in the continuation	of Box C. See patent family annex.
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·* de	ocument defining the general state of the art which is not on be part of particular relevance	date and not in conflict with the application but cited to understand the principle or theory underlying the invention
	riler document published on or after the international filing	a data "X" document of particular releases the state of facilities and
• de	etiment which may throw doubts on priority claim(s) or	considered novel or cannot be considered to involve an inventive step
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	, D.C. 20231	ROBERT GERSTL
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INTERNATIONAL SEARCH REPORT

International Application No. PCT/US93/07173

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No. 1-26 1-26	
Y.	The Journal of Antibiotics, Volume 40, issued June 1987, K. Nemoto, "Enhancement of colony Formation of mouse bone marrow cells by ubenimex", pages 894-898, see entire document.		
Y	Cancer Immunology Immunotherapy, Volume 29, Issued April 1989, F. Abe et al., "Chemoimmunotherapy with cyclophosphamide and bestatin in experimental metastasis in mice", pages 231-236, see entire document.		
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INTERNATIONAL SEARCH REP RT

International application No. PCT/US92/06047

A. CLASSIFICATION OF SUBJECT MATTER: US CL :

514/19, 365, 370, 377, 392, 397, 398, 400; 546/175, 278; 548/193, 194, 200, 204, 233, 236, 312.7, 315.1, 328.5, 332.5, 335.5, 338.1, 338.5

B. FIELDS SEARCHED Minimum documentation searched Classification System: U.S.

514/19, 365, 370, 377, 392, 397, 398, 400; 546/175, 278; 548/193, 194, 200, 204, 233, 236, 312.7, 315.1, 328.5, 332.5, 335.5, 338.1, 338.5